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PERGAMON PRESS LTD.

OXFORD LONDON NEW YORK PARIS

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STUDIES ON THE STEROIDAL COMPONENTS OF DOMESTIC PLANTS—XXI[1]

THE STRUCTURE OF KOGAGENIN (PART 3) ON ANHYDROKOGAGENIN

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(*Received* 26 *January* 1960)

Abstract—In an earlier paper[5] of this series, we assigned the position of the double bond in anhydrokogagenin, a dehydration product of kogagenin, at C-5 and 6 tentatively. This has now been confirmed to be located at C-4 and 5 from the results of the epoxide formation, manganese dioxide oxidation and the glycol fission reaction. It has been found that the reaction of anhydrokogagenin with acetone containing a small amount of *p*-toluenesulphonic acid gives an allylic rearrangement product together with the normal acetonide.

KOGAGENIN is a tetrahydroxysapogenin isolated from the epigeous part of *Dioscorea Tokoro*, Makino and its structure was established as 25D-spirostane-1β,2β,3α,5β-tetrol (Ia).[1,2]

During the course of investigation of this structure, anhydrokogagenin triacetate (IIb), m.p. 171–173°, which was obtained by dehydration of kogagenin triacetate with thionyl chloride in pyridine, played an important role in the structural elucidation of kogagenin.

In the earlier paper,[2] the double bond in anhydrokogagenin triacetate (IIb) was assigned tentatively to the C-5 position merely from the fact that anhydrokogagenin (IIa) gave a negative Rosenheim test. Little attention was paid as to whether its double bond was located at C-4 or at C-5, because this was unnecessary for the elucidation of the structure of kogagenin.

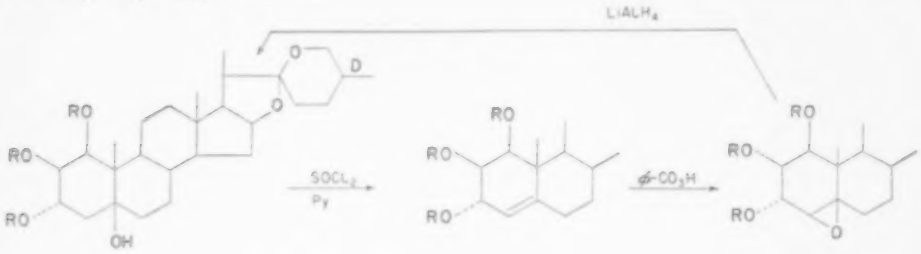
The results of epoxidation of IIb, as described below, showed the possibility of the double bond being at C-4 and prompted investigation to clarify the position of this double bond in anhydrokogagenin (IIa).

Treatment of anhydrokogagenin triacetate (IIb) with perbenzoic acid afforded an epoxide, m.p. 151–153°, which was reduced with lithium aluminium hydride and yielded kogagenin, having the 5β-hydroxyl group as established in the preceding paper,[1] as a sole product.

From these findings it was assumed that the parent triacetate-epoxide must be the β-epoxide. Moreover, in view of the fact that the reduction of steroidal 5β,6β-epoxides with lithium aluminium hydride affords a quantity of 5β-alcohols in addition to 6β-alcohols[3] while 4β,5β-epoxides give only 5β-alcohols,[4] the above results suggested that the double bond in anhydrokogagenin triacetate (IIb) may be located at C-4.

[1] Part XX: T. Kubota, *Chem. Pharm. Bull.* **7**, 898 (1959).
[2] K. Takeda, T. Kubota and A. Shimaoka, *Tetrahedron* **7**, 62 (1959).
[3] Pl. A. Plattner, H. Heusser and M. Feurer, *Helv. Chim. Acta* **32**, 587 (1949): A. S. Hallsworth and H. B. Henbest, *J. Chem. Soc.* 4604 (1957).
[4] Pl. A. Plattner, H. Heusser and A. B. Kulkarni, *Helv. Chim. Acta* **31**, 1885 (1948): C. W. Shoppee, M. E. H. Howden, R. W. Killick and G. H. R. Summers, *J. Chem. Soc.* 630 (1959).

On the other hand, Henbest and Wilson[5] reported that the epoxide formation of cyclic allylic alcohols occurs from the same side of this hydroxyl group. On the basis of this fact, perbenzoic acid oxidation of free anhydrokogagenin (IIa) was carried out in order to obtain the anticipated α-epoxide, contrary to the case of IIb. Although there was obtained a single epoxide melting at 274–276°, this product was identical in all respects with the β-epoxide (IIIa) which was obtained on saponification of the triacetate-β-epoxide (IIIb) prepared from IIb. Therefore, epoxidation of anhydrokogagenin (IIa) gave no support to the possibility of this compound possessing the allylic hydroxyl function.



Ia R=H
b R=Ac

IIa R=H
b R=Ac

IIIa R=H
b R=Ac

CHART I

In order to determine the presence of an allylic hydroxyl group in IIa, this was subjected to manganese dioxide oxidation. When progress of the oxidation was checked by ultra-violet spectra, in the early stage (30 min) of this experiment, it showed a maximum of ε 7000 at 244 mμ indicating the formation of the expected Δ^4-3-ketone system. The intensity of this absorption did not increase with the lapse of oxidizing time and a new absorption at 282 mμ of low intensity appeared. After the oxidation was allowed to proceed for a longer time (6 hr), the absorption at 244 mμ disappeared and that at 282 mμ rose to ε 5600. This observation suggested that the primary product considered to be a Δ^4-3-one derivative must be further attacked by manganese dioxide.

When manganese dioxide oxidation of anhydrokogagenin (IIa) was stopped after 45 min at 0°, a product expected to be the Δ^4-3-ketone (IV), m.p. 202–204°, showing λ_{max} 244 mμ (log ε 4·10) could be isolated with purification by chromatography on silica gel. This product was identical with the dihydroxy-Δ^4-3-ketone (IV) which was obtained from the previously reported compound (VI)[2] by acid hydrolysis.

Since it has now been proved that the primary oxidation product is the dihydroxy-Δ^4-3-ketone (IV), the further oxidation product showing absorption at 282 mμ was studied. Rosenkranz *et al.*[6] reported that, when Δ^4-3-ketones or Δ^5-3β-ols were treated with manganese dioxide for a long time, each compound afforded $\Delta^{4,6}$-diene-3-ones having the maximum at 284 mμ. The oxidation product of IIa showed

[5] H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.* 1958 (1957).
[6] F. Sondheimer, C. Amendolla and G. Rosenkranz, *J. Amer. Chem. Soc.* **75**, 5932 (1953).

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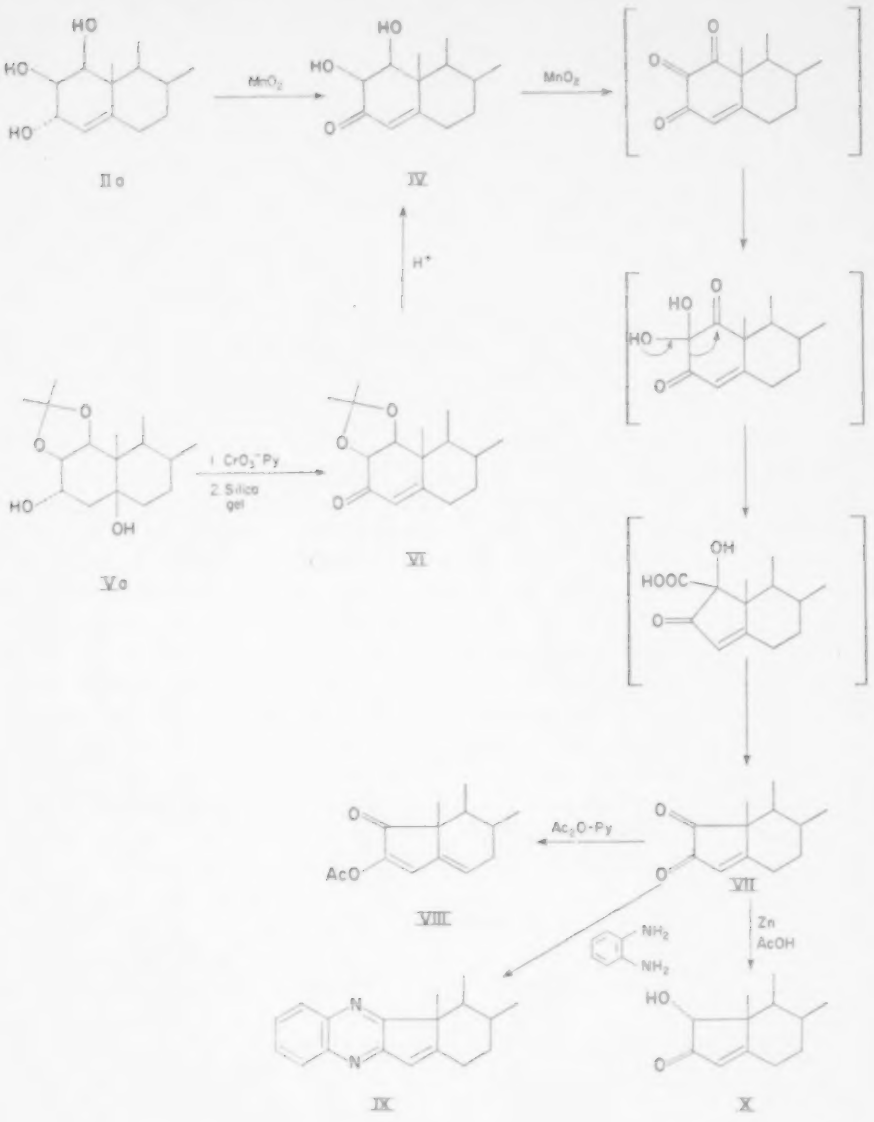

CHART 2

constants differing from those of the expected $\Delta^{4,6}$-diene-3-one compound, as described below. The analytical values agreed with an empirical formula $C_{26}H_{36}O_4$ and suggest the loss of CH_4O from the primary product (IV). Its ultra-violet spectrum showed absorption maxima at 230 and 282 mμ (log ε 3·60 and 3·75, respectively) and the infra-red spectrum exhibited strong bands at 5·69, 5·80 and 6·22 μ but no hydroxyl band. From the basis of these data, the structure of this compound was presumed

to be the five-membered ene-dione (VII). This was supported by the following chemical behaviour: (a) acetylation with refluxing acetic anhydride–pyridine gave an enol acetate (VIII) showing the ultra-violet absorption at 299 mμ (log ε 3·97); (b) reaction with *o*-phenylenediamine afforded a quinoxaline derivative (IX), $C_{32}H_{40}O_2N_2$; (c) reduction with zinc and acetic acid gave an unsaturated ketol (X) which showed ultra-violet absorption maximum at 237 mμ (log ε 4·16), the infra-red bands at 2·86 μ (hydroxyl) and at 5·85 and 6·17 μ (five-membered unsaturated ketone), and a positive triphenyltetrazolium test. The formation of the five-membered ring in VII perhaps resulted from hydration of a triketone, which would be probably produced by oxidation of the ketol function in the dihydroxy-Δ^4-3-ketone (IV) with manganese dioxide, followed by the benzilic acid rearrangement as shown in Chart 2. However such compounds were hitherto unknown and the elucidation of the above-mentioned ultra-violet absorption remained doubtful.

From the above results it became certain that IIa possesses the double bond at C-4. In order to obtain more convincible evidence for the structure IIa of anhydrokogagenin, cleavage reaction of the double bond was carried out. Anhydrokogagenin triacetate (IIb) was *cis*-hydroxylated to a pentol triacetate (XI) with osmium tetroxide as described previously.[2] The newly introduced glycol function in XI has been assigned the β-configuration by analogy to the results on the above-mentioned epoxide formation and catalytic reduction.[2] When the pentol triacetate (XI) was treated with lead tetracetate, one equivalent of the reagent was consumed to yield the 4,5-secoaldehyde-ketone (XIII), m.p. 187–190°.[7] By oxidation with chromium trioxide, this aldehyde-ketone (XIII) led to an amorphous triacetoxy-keto-acid (XVb). When XVb was treated with a 1 per cent methanolic potassium hydroxide solution, besides an amorphous product assumed to be a trihydroxy-keto-acid (XVa), a small amount of a neutral product, m.p. 156–158°, having an empirical formula $C_{23}H_{36}O_3$ was obtained. The infra-red spectrum of this neutral product showed, except for an absorption at 5·84 μ corresponding to a six-membered ketone, neither another carbonyl band nor a hydroxyl band. Also, treatment of this compound with hydroxylamine gave an oxime, $C_{23}H_{37}O_3N$, m.p. 217°. Based on the above results the structure of this ketone has been assigned to be a des-A-5-ketone (XVI) which may be produced via retro-aldol reaction[8] of the trihydroxy-4,5-secoketo-acid (XVa) derived from the Δ^4-compound. When the triacetoxy-keto-acid (XVb) was treated with alkali under more vigorous conditions, it gave the same XVI in good yield, as would be expected. The methyl group at C-10 in XVI has been assigned to the more stable α-configuration (i.e. equatorial) by the analogous example.[9]

Furthermore, the pentol (XII) prepared from saponification of XI underwent glycol fission with lead tetracetate and yielded the expected trisnor-1,5-secoaldehyde-ketone (XIV), $C_{24}H_{36}O_4$, m.p. 222–225° (decomp). Since it is well-known that such formyl ketones are sensitive to alkali or acid,[10] by treatment with alcoholic potassium hydroxide solution, XIV was easily converted to the above-mentioned des-A-5-ketone (XVI).

These results have now confirmed that the double bond in anhydrokogagenin is

[7] This compound was amorphous in the previous experiment.[2]
[8] C. Djerassi and H. G. Monsimmer, *J. Amer. Chem. Soc.* **79**, 2901 (1957).
[9] J. Castells, E. R. E. Jones, G. D. Meakins and R. W. J. Williams, *J. Chem. Soc.* 1159 (1959).
[10] A. L. Wilds and C. Djerassi, *J. Amer. Chem. Soc.* **68**, 1715 (1946).

located at C-4. Therefore, the formulae described in the previous paper for anhydrokogagenin and its derivatives should now be corrected to Δ^4-25D-spirostene-1β,2β,3α-triol (IIa) and its derivatives. Assuming that ionic elimination readily occurs between *trans*-diaxial function, it seems to be reasonable that dehydration of kogagenin triacetate (Ib) with thionyl chloride–pyridine furnished exclusively the Δ^4-compound (IIb), because the 5β-hydroxyl group is axial to ring A but equatorial to ring B.

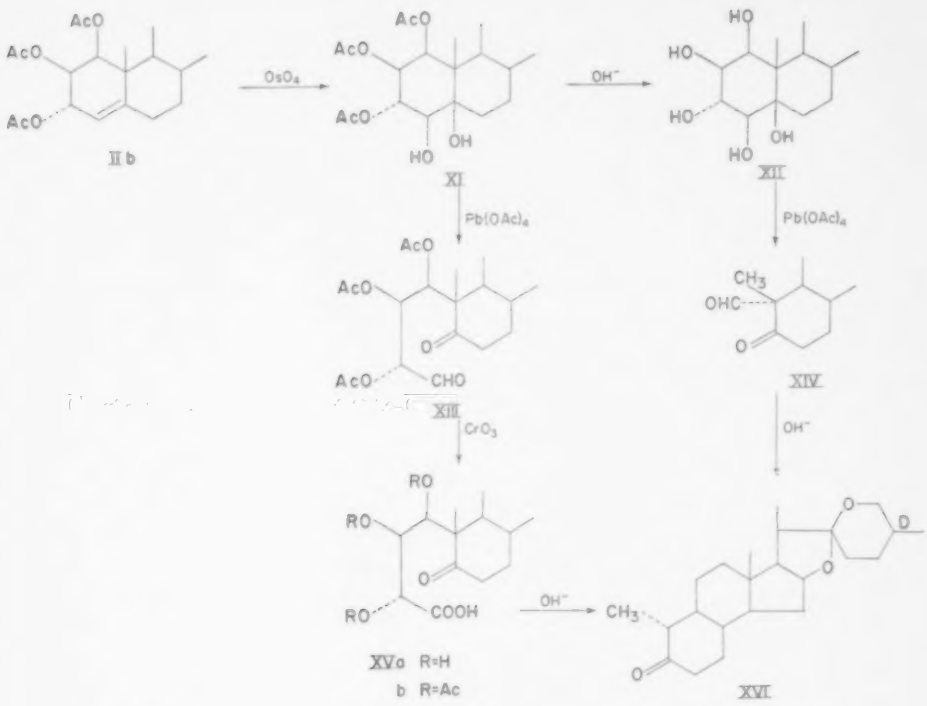

CHART 3

At present, with the constitution of anhydrokogagenin having been established, it is more difficult to understand why the so-called anhydrokogagenin acetonide, which was obtained on treatment of IIa with acetone and *p*-toluenesulphonic acid, was unaffected with chromium trioxide–pyridine, chromium trioxide–acetone–sulphuric acid or by the Oppenauer oxidation, as described earlier.[2] Thus, in order to clarify this question, the reaction of acetonide formation was reinvestigated.

Anhydrokogagenin (IIa) was refluxed in acetone containing a small amount of *p*-toluenesulphonic acid. Chromatography of the product over alumina afforded, as described in the previous experiment,[2] a small amount of the acetonide diene (XVII) and a main product (A), m.p. 208–210°, previously assigned to be anhydrokogagenin acetonide (XVIIIa) on the basis of its analytical values and infra-red spectrum. Further elution of the above chromatography gave another isomer (B) having a melting point of 227–230°. The analytical values for the isomer (B) are in

good agreement with the formula $C_{30}H_{46}O_5$ corresponding to XVIIIa. Its infra-red spectrum showed the bands at 2·83 μ (hydroxyl), 6·00 μ (double bond) and at 7·98, 8·12 and 8·23 μ (acetonide) and satisfied the structure XVIIIa. The ultra-violet spectra of the two isomers, (A) and (B), were examined. The intensity of the absorption maximum at 206 mμ due to the double bond, for the isomer (A) was merely ε 880, in contrast with the ε 6050 and ε 5100 for anhydrokogagenin (IIa) and the isomer

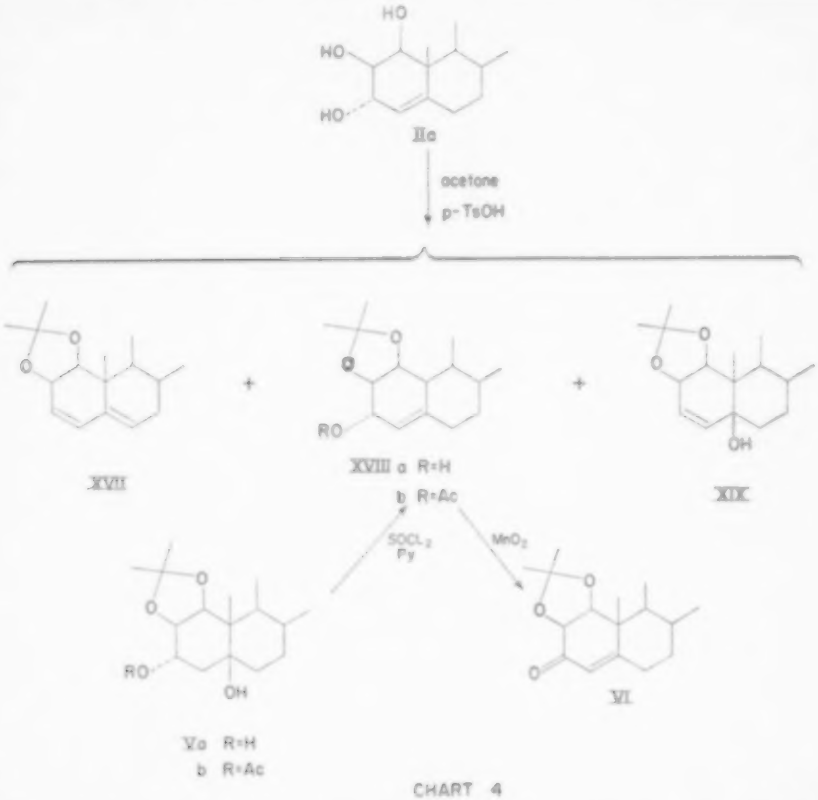

CHART 4

(B), respectively. This observation suggested that the double bond in the isomer (A) may be a disubstituted one.[11] When the infra-red spectrum of each isomer was minutely determined with KBr prism, the above assumption was supported by the facts that the isomer (B) showed the absorption band at 12·18 μ corresponding to a trisubstituted double bond while the isomer (A) exhibited the band at 14·41 μ due to a *cis*-disubstituted double bond. According to these facts it is deduced that the isomer (A) previously presumed to be XVIIIa has the structure XIX in which allylic rearrangement and acetonide formation occurred simultaneously by refluxing of IIa and *p*-toluenesulphonic acid in acetone. The newly isolated isomer (B) is concluded to have the structure XVIIIa expected for the normal acetonide of IIa. This has been proved by the identification with a sample prepared by the following route, i.e. acetylation of kogagenin acetonide (Va) followed by dehydration of the C_5-hydroxyl

[11] P. Bladon, H. B. Henbest and G. W. Wood, *J. Chem. Soc.* 2737 (1952).

group with thionyl chloride-pyridine and saponification. This compound was also oxidized smoothly with manganese dioxide to the acetonide-Δ^4-3-ketone (VI). Moreover, the isomer (A) was resistant to manganese dioxide oxidation or acetylation by refluxing acetic anhydride-pyridine and the starting material was recovered almost quantitative, as would be expected.

Although there are very few examples on the allylic rearrangement in the steroid field,[12] it is well-known that acidic treatment of Δ^4-sterols readily causes $\Delta^{3,5}$-diene formation.[13] It is interesting that the above-mentioned reaction of IIa resulted chiefly in allylic rearrangement than in dehydration.

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EXPERIMENTAL

All melting points are uncorrected. Ultra-violet absorption spectra were taken with a Beckman Model DU Spectrophotometer. Infra-red spectra were measured using a Koken Infra-red Spectrophotometer Model DS 301. Rotations were determined with a Roudolf Photoelectric Polarimeter Model 200.

Epoxidation of anhydrokogagenin triacetate (IIb)

To a solution of IIb[3] (1·658 g) in chloroform (3 ml) was added a 0·46 M solution (12 ml) of perbenzoic acid in chloroform. After standing at room temp (15–21°) for 48 hr, the mixture was diluted with ether, washed with NaOH solution and water, and dried. The solvent was removed under reduced pressure leaving an oil (1·7 g) which was chromatographed on alumina (30 g). The fractions (1·294 g), eluted with a mixture of petroleum ether and benzene (1:1), were crystallized from aqueous methanol to prisms (1·00 g) of 1*β*,2*β*,3*α*-*triacetoxy*-4*β*,5*β*-*epoxy*-25D-*spirostane* (IIIb), m.p. 149–152°, $[\alpha]_D$ −3° (*c* 0·60, chloroform). (Found: C, 67·18; H, 8·22. $C_{33}H_{46}O_9$ requires: C, 67·32; H, 8·22%).

The further elution of the above chromatography with benzene and with chloroform gave an oil (390 mg) showing a hydroxyl band in the infra-red spectrum. Saponification with refluxing methanolic KOH solution gave 1*β*,2*β*,3*α*-*trihydroxy*-4*β*,5*β*-*epoxy*-25D-*spirostane* (IIIa, described below) in crystalline form.

Reduction of 1*β*,2*β*,3*α*-*triacetoxy*-4*β*,5*β*-*epoxy*-25D-*spirostane* (IIIb) *with lithium aluminium hydride*

To a suspension of lithium aluminium hydride (200 mg) in dry ether (30 ml), a solution of IIIb (215 mg) in dry benzene (30 ml) was added dropwise under stirring. The mixture was heated under reflux (52°) for 3 hr. After cooling, a small portion of water was added carefully to decompose the complex and then the mixture was acidified with dil HCl to dissolve an amorphous metal hydroxide. The precipitated crystals were collected by filtration, washed with water and dried yielding scales (168 mg), m.p. 298–303° (decomp). The organic layer of the filtrate gave only 4 mg of the organic material. The combined product (172 mg) was acetylated by refluxing with acetic anhydride and pyridine. The crude acetate was chromatographed over alumina (7 g). The fractions (15 mg) eluted with petroleum ether–benzene (1:3) were crystallized from methanol to scales, m.p. 167–170°, which was identical with anhydrokogagenin triacetate (IIb). The eluates with benzene and with benzene–chloroform (19:1 to 4:1) were combined and recrystallization of the fraction (190 mg) from methanol furnished prisms (144 mg), m.p. 248–251°, which showed no depression on admixture with an authentic sample of kogagenin triacetate (Ib).[3] Infra-red spectra of these samples were identical.

Further elution of the above chromatography with chloroform and chloroform–methanol (1:1) afforded only an impure material (13 mg).

1*β*,2*β*,3*α*-*Trihydroxy*-4*β*,5*β*-*epoxy*-25D-*spirostane* (IIIa)

(a) *By saponification of* 1*β*,2*β*,3*α*-*triacetoxy*-4*β*,5*β*-*epoxy*-25D-*spirostane* (IIIb). The aforementioned IIIb (100 mg) prepared by epoxidation of IIb was refluxed in 10% methanolic KOH

[12] B. Pelc, *Coll. Czech. Chem. Comm.* **22**, 1457 (1957); R. E. Ireland, T. I. Wrigley and W. G. Young, *J. Amer. Chem. Soc.* **80**, 4604 (1958).
[13] H. McKennis, Jr. and G. W. Gaffney, *J. Biol. Chem.* **175**, 217 (1948); W. G. Danben and L. F. Eastham, *J. Amer. Chem. Soc.* **73**, 3260 (1951).

solution (10 ml) for 2 hr. The cooled reaction mixture was diluted with water and the precipitate was filtered and recrystallized from chloroform–methanol giving small plates of IIIa, m.p. 273–275°, $[\alpha]_D$ −63° (*c* 0·99, 1:1 chloroform–methanol mixture). (Found: C, 70·31; H, 9·11. $C_{27}H_{42}O_6$ requires: C, 70·10; H, 9·15%).

(b) *By epoxidation of anhydrokogagenin* (IIa). To a 0·21 M solution (2·5 ml) of perbenzoic acid in chloroform, IIa (200 mg) was added. When the solution was stored in a refrigerator for 48 hr, a precipitate appeared. Filtration and washing with chloroform furnished needles (114 mg), m.p. 266–270°, which was recrystallized from ethyl acetate–methanol giving small plates of IIIa, m.p. 272–274°, $[\alpha]_D$ −61° (*c* 1·00, 1 : 1 chloroform–methanol mixture). The m.p. was not depressed on admixture with a specimen prepared by the method (a) and the infra-red absorption spectra of the two samples were identical. (Found: C, 70·18; H, 9·05. Calc. for $C_{27}H_{42}O_6$: C, 70·10; H, 9·15%).

From the filtrate the additional IIIa (67 mg) was obtained.

TABLE 1

Min	log *ε*	
	$\lambda_{224\ m\mu}$	$\lambda_{282\ m\mu}$
10	3·84	2·73
20	3·84	3·02
30	3·82	3·15
60	3·79	3·36
120	3·76	3·50
240	3·57	3·72
360	3·45	3·74
480	3·45	3·76

Manganese dioxide oxidation of anhydrokogagenin (IIa)

A solution of IIa (100 mg) in chloroform (10 ml) was shaken at room temp (30° ± 1°) with manganese dioxide (1·0 g) prepared by Rosenkranz's method.[14] Small quantities of the reaction mixture were withdrawn at intervals and freed from the manganese dioxide and solvent. These samples were determined by ultra-violet spectrum in a 95% ethanolic solution with the result as shown in Table 1.

Δ^4-25D-*Spirostene*-1β,2β-*diol*-3-*one* (IV)

(a) *By manganese dioxide oxidation of anhydrokogagenin* (IIa). A solution of IIa (110 mg) in chloroform (11 ml) was shaken with manganese dioxide (1·1 g) for 45 min under cooling in an ice-bath. After removal of the manganese dioxide and the solvent, the crystalline residue (85 mg) was chromatographed on silica gel (2 g). Elution with benzene–chloroform (9:1 to 4:1) gave yellow crystals (8 mg) of the further oxidized product (VII) described below. The next fractions (50 mg) eluted with chloroform, on crystallization from aqueous acetone, furnished long, silky needles, m.p. 202–204°, λ_{max}^{EtOH} 244 mμ (log *ε* 4·10). No depression in m.p. was observed on admixture with an authentic sample of the dihydroxy-Δ^4-3-ketone (IV) prepared by the method (b) described below and the infra-red spectra of these two substances were identical.

The 1:1 chloroform–methanol eluate (25 mg) of the above chromatography gave the starting material (IIa), m.p. 240–243° (decomp).

(b) *By acidic hydrolysis of* Δ^4-25D-*spirostene*-1β,2β-*diol*-3-*one acetonide* (VI). The acetonide (VI, 135 mg), prepared by oxidation of kogagenin acetonide followed by dehydration as described previously,[2] was refluxed for 30 min in methanol (10 ml) containing conc HCl (1 drop). The mixture was diluted with ether, washed 3 times with water and dried. After removal of the solvent, the crystalline residue was chromatographed on silica gel (3 g). The fractions (15 mg) eluted with benzene–chloroform (4:1) furnished, on recrystallization from acetone, $\Delta^{1,4}$-25D-spirostadien-2-ol-3-one[2] as scales, m.p. 234–237°. The eluate (111 mg) with benzene–chloroform and with chloroform

[14] O. Mancera, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.* 2189 (1953).

was crystallized from aqueous acetone to long needles of IV, m.p. 202–204°. For analysis, the substance was recrystallized once more from the same solvent and dried *in vacuo* for 5 hr at 110°: $[\alpha]_D$ −141° (*c* 0·66, chloroform), λ_{max}^{EtOH} 244 mμ (log ε 4·10). (Found: C, 73·11: H, 9·04. $C_{27}H_{46}O_5$ requires: C, 72·94; H, 9·07%).

The by-product (A-*nor*-$\Delta^{3(5)}$-25D-*spirostene*-1,2-*dione*, VII) *of manganese dioxide oxidation of anhydrokogagenin* (IIa)

(a) *Isolation of the product* (VII). A mixture of IIa (300 mg) and manganese dioxide (3·0 g) in chloroform (30 ml) was stirred for 6 hr at room temp. The dioxide was filtered and the filtrate was evaporated to dryness and chromatographed over silica gel (3 g). Elution with benzene and recrystallization of the eluate (188 mg) from chloroform–methanol mixture gave yellow plates (140 mg) of VII, m.p. 228–230° (decomp), $[\alpha]_D$ −118° (*c* 0·75, chloroform), negative ferric chloride reaction; λ_{max}^{EtOH} 230, 282 mμ (log ε 3·60, 3·75); λ_{max}^{KOH} 345 mμ (log ε 3·70); λ_{max}^{Nujol} 5·69, 5·80, 6·22 μ, no hydroxyl absorption. (Found: C, 75·71, 75·62; H, 8·81, 8·72. $C_{26}H_{36}O_4$ requires: C, 75·69; H, 8·80%).

(b) *Acetylation of* VII. A mixture of the foregoing VII (100 mg), acetic anhydride (2 ml) and pyridine (2 ml) was heated under reflux for 2 hr. The product, extracted with ether in the usual manner, was recrystallized from ethyl acetate–alcohol mixture giving colourless prisms of the *enol acetate* (VIII), m.p. 222–224°, $[\alpha]_D$ +55° (*c* 1·01, chloroform); λ_{max}^{EtOH} 299 mμ (log ε 3·97); λ_{max}^{Nujol} 5·62, 8·37–8·53 μ (enol acetate), 5·84, 5·97, 6·25 μ (five-membered conj. dienone). (Found: C, 73·77; H, 8·49. $C_{28}H_{38}O_5$ requires: C, 73·98; H, 8·43%).

(c) *Treatment of* VII *with o-phenylenediamine*. The above VII (100 mg) in alcohol (20 ml) was refluxed with *o*-phenylenediamine (100 mg) for 2 hr and then concentrated until crystals started separating. After cooling the crystals (87 mg), m.p. 260–265°, were collected and recrystallized twice from chloroform–alcohol to give pale yellow needles of the *quinoxaline derivative* (IX), m.p. 272–274° (decomp), $[\alpha]_D$ −191° (*c* 1·03, chloroform); λ_{max}^{EtOH} 223, 260, 266, 338, 354 mμ (log ε 4·39, 4·35, 4·34, 4·13, 4·11); λ_{max}^{Nujol} 6·17, 6·22, 6·30, 6·36, 13·12 μ. (Found: C, 79·24; H, 8·30; N, 5·51. $C_{32}H_{40}O_2N_2$ requires: C, 79·30; H, 8·32; N, 5·78%).

(d) *Treatment of* VII *with zinc and acetic acid*. A yellow solution of VII (100 mg) in acetic acid (20 ml) was decolourized as soon as zinc dust (1·0 g) was added. After refluxing for 3 hr, zinc was removed by decantation and ether and water were added to the solution. The ether layer was washed, dried and evaporated to dryness *in vacuo*. The residue was recrystallized twice from methanol yielding needles (30 mg) of the *unsaturated ketol* (X), m.p. 233–235°, $[\alpha]_D$ −104° (*c* 0·96 chloroform); λ_{max}^{EtOH} 237 mμ (log ε 4·16), λ_{max}^{Nujol} 2·86 μ (OH), 5·85, 6·17 μ (five-membered conj. unsat. ketone). (Found: C, 75·67; H, 9·47. $C_{26}H_{38}O_4$ requires: C, 75·32; H, 9·24%).

Treatment of 25D-*spirostane*-1β,2β,3α,4β,5β-*pentol* 1β,2β,3α-*triacetate* (XI) *with lead tetracetate*

The pentol triacetate (XI), m.p. 252–254°, was prepared on treatment of IIb with osmium tetroxide as described previously.[3] To a solution of XI (430 mg) in acetic acid (10 ml) was added lead tetracetate–acetic acid (29·68 mg/ml) solution (21 ml). After standing overnight at room temp, iodometric determination of the reaction mixture showed that one equivalent of the reagent was consumed. The reaction mixture was diluted with water and extracted with ether. The extract was washed with sodium carbonate solution and water, dried and evaporated. Crystallization of the glassy residue (420 mg) from ether-*n*-pentane mixture gave the 4,5-*secoaldehyde-ketone* (XIII) as needles (389 mg), m.p. 184–187°. The pure sample showed the following constants: m.p. 187–190°, $[\alpha]_D$ −90° (*c* 0·98, chloroform); λ_{max}^{Nujol} 5·68, 5·73 μ (acetate and aldehyde), 5·87 μ (ketone), no hydroxyl band. (Found: C, 65·88; H, 8·13. $C_{33}H_{48}O_{10}$ requires: C, 65·54; H, 8·00%).

Oxidation of the 4,5-*secoaldehyde-ketone* (XIII)

To a solution of XIII (300 mg) in 90% acetic acid (10 ml), a solution (1·94 ml) of chromium trioxide in 90% acetic acid (20 mg/ml) was added. After standing for 1 hr at room temp, the reaction mixture was diluted with water and extracted with chloroform–ether (4:1) mixture. The solvent layer was washed with water and the acidic substances extracted with sodium carbonate solution. The alkaline solution was acidified with dil HCl and extracted with ether. The ether solution was washed, dried and evaporated leaving an oil (297 mg) of the *triacetoxy-keto-acid* (XVb) which was not obtained in crystalline form.

Alkaline treatment of the triacetoxy-keto-acid (XVb)

(a) *With 1% methanolic potassium hydroxide solution.* When the foregoing XVb (297 mg) was dissolved in a 1% methanolic KOH solution (20 ml), the solution turned to yellow. After refluxing 1 hr, the mixture was diluted with water and the methanol was removed *in vacuo*. The alkaline solution was extracted with ether and the extract was washed with water, dried with sodium sulphate and evaporated to dryness. Crystallization of the oily residue (72 mg) from methanol gave needles (27 mg), m.p. 145–148°, which was purified by chromatographed over alumina followed by recrystallization from methanol yielding scales of *des*-A-25D-*spirostan*-5-*one* (XVI), m.p. 156–158°, $[\alpha]_D$ −84° (*c* 0·90, chloroform); λ_{max}^{Nujol} 5·84 μ (C=O), no hydroxyl absorption. (Found: C, 76·82; H, 10·08. $C_{33}H_{56}O_3$ requires: C, 76·62; H, 10·07%). Treatment of this XVI (48 mg) with hydroxylamine by the usual manner gave needles (from alcohol) of the *oxime* (34 mg), m.p. 217°. (Found: C, 73·87; H, 10·03; N, 3·68. $C_{33}H_{57}O_3N$ requires: C, 73·56; H, 9·93; N, 3·73%).

The alkaline solution after separation of the neutral fraction was acidified with dil HCl and extracted with ether. The ether extract was washed with water, dried and evaporated leaving a gummy residue (177 mg) presumed to be the *trihydroxy-keto-acid* (XVa). This acid was esterified with ethereal diazomethane to the oily *methyl ester*. The infra-red spectrum satisfied the given structure as follows: λ_{max}^{Nujol} 2·86–2·96 μ (OH), 5·75 μ (ester), 5·85 μ (ketone). However this trihydroxy-keto-ester was recovered unchanged after treatment with excess lead tetracetate in acetic acid or with periodic acid in 85% methanol for 20 hr at room temp.

(b) *With 5% alcoholic potassium hydroxide solution.* The oily triacetoxy-keto-acid (XVb, 153 mg) derived from XIII (150 mg) was heated on a steam bath for 1 hr with a 5% alcoholic KOH solution (20 ml). The reaction mixture was diluted with water and extracted with ether. The ether layer was treated in the usual manner and the crude substance (77 mg) was recrystallized from methanol to scales (50 mg) of m.p. 156–158°. Identity with a sample of the des-A-ketone (XVI) was established by the infra-red and mixed m.p. determination.

25D-*Spirostane*-1β,2β,3α,4β,5β-*pentol* (XII)

The pentol triacetate (XI, 450 mg) was dissolved in methanol (30 ml) by warming. When KOH (450 mg) in water (1 ml) was added to this solution, precipitation immediately occurred. The mixture was refluxed for 4 hr with this precipitate remaining. After cooling the crystals were filtered, washed with methanol and water, and recrystallized from chloroform–methanol to give the pentol (XII) decomposing gradually above 330°; yield 326 mg. (Found: C, 67·77; H, 9·28. $C_{27}H_{44}O_7$ requires: C, 67·47; H, 9·23%).

Treatment of 25D-*spirostane*-1β,2β,3α,4β,5β-*pentol* (XII) *with lead tetracetate*

To a solution of lead tetracetate (1·6 g), acetic acid (40 ml) and chloroform (40 ml), XII (220 mg) was added. After the solution was allowed to stand at room temp overnight, water and ether were added. The ether extract was washed with sodium carbonate solution and water, dried and evaporated under reduced pressure. The crystalline residue (189 mg) was recrystallized from chloroform-methanol yielding prisms (117 mg) of the A-*trisnor*-1,5-*secoaldehyde-ketone* (XIV), m.p. 220–224° (decomp). After further recrystallization the pure sample showed the following constants: m.p. 222–225° (decomp), $[\alpha]_D$ −99° (*c* 0·97, chloroform); λ_{max}^{Nujol} 5·78 μ (aldehyde), 5·91 μ (ketone), no hydroxyl absorption. (Found: C, 73·98; H, 9·35. $C_{24}H_{36}O_4$ requires: C, 74·19; H, 9·34%).

Alkaline treatment of the A-trisnor-1,5-*secoaldehyde-ketone* (XIV)

A mixture of XIV (40 mg) and KOH (100 mg) in alcohol (5 ml) was refluxed for 30 min in an atmosphere of nitrogen. The solution was diluted with ether, washed with water and dried. After removal of the solvent, the crystalline residue (24 mg) was recrystallized from methanol to give scales (20 mg) of the des-A-ketone (XVI), m.p. 156–158°.

Treatment of anhydrokogagenin (IIa) *with acetone and* p-*toluenesulphonic acid*

A solution of IIa (139 mg) and *p*-toluenesulphonic acid dihydrate (15 mg) in acetone (30 ml) was refluxed for 5 hr and then allowed to stand at room temp overnight. The reaction mixture was neutralized with sodium bicarbonate solution and concentrated to about one third of the initial volume under reduced pressure. The concentrated solution was diluted with water and extracted

with ether. The extract was washed with water and dried. After removal of the solvent, the crystalline residue (156 mg) was chromatographed on alumina (5 g). The fraction (14 mg) eluted with petroleum ether–benzene (9:1) gave, on crystallization from methanol, the acetonide-$\Delta^{3,5}$-diene (XVII),[2] m.p. 162–165°.

Elution with petroleum ether–benzene (4:1) and with benzene and recrystallization of the eluate (79 mg) from methanol furnished needles (66 mg), m.p. 208–210°, $[\alpha]_D$ −58° (*c* 1·00, chloroform), corresponding to a specimen reported to be anhydrokogagenin acetonide in the previous paper.[2] The structure of this compound was assigned Δ^3-25D-*spirostene*-1β,2β,5ξ-*triol* 1,2-*acetonide* (XIX) based on the following constants: λ_{max}^{EtOH} 206 mμ (log ϵ 2·94); λ_{max}^{Nujol} 2·84 μ (OH), 8·10 μ (—O—), 6·03, 14·41 μ (*cis*—CH=CH—).

This acetonide-Δ^3-5-ol (XIX) was recovered unchanged after treatment with manganese dioxide in chloroform for 6 hr and it was not acetylated by refluxing for 1 hr with acetic anhydride in pryidine.

Further elution of the above chromatography with benzene–chloroform and with chloroform gave the crystalline eluate (51 mg). Recrystallization from methanol gave needles (34 mg), m.p. 202–213°, which was recrystallized twice from the same solvent to yield the pure sample, m.p. 226–230°, $[\alpha]_D$ −7° (*c* 0·88, chloroform); λ_{max}^{EtOH} 206 mμ (log ε 3·73); λ_{max}^{Nujol} 2·83 μ (OH), 7·98, 8·12, 8·23 μ (—O—), 6·00, 12·18 μ (>C=CH—). (Found: C, 74·03; H, 9·81. $C_{30}H_{46}O_5$ requires: C, 74·03; H, 9·53%). No depression was observed on mixed m.p. with a sample of Δ^4-25D-*spirostene*-1β,2β,3α-*triol* 1,2-*acetonide* (XVIIIa), m.p. 227–230°, prepared by the following method, and the infra-red absorption spectra of the two specimens were identical.

Preparation of anhydrokogagenin acetonide (XVIIIa) *from kogagenin acetonide* (Va)

A mixture of kogagenin acetonide (Va,[2] 230 mg), acetic anhydride (2·5 ml) and pyridine (5 ml) was allowed to stand at room temp for 48 hr. The product, extracted with ether in the usual way, was recrystallized from methanol to give *kogagenin acetonide* 3-*acetate* (Vb) as prisms (225 mg), m.p. 234–237°, $[\alpha]_D$ +13° (*c* 0·98, chloroform). (Found: C, 70·68; H, 9·40. $C_{32}H_{50}O_7$ requires: C, 70·30; H, 9·22%).

To a solution of the foregoing Vb (200 mg) in pyridine (2 ml), thionyl chloride (0·3 g) in pyridine (3 ml) was added dropwise under cooling in an ice-bath. After standing for 45 min at 0° the excess reagent was destroyed with ice and the product was extracted with ether. The extract was washed with dil HCl, sodium bicarbonate solution and water, dried and evaporated leaving the crystalline residue (194 mg), m.p. 184–187°, which was recrystallized twice from methanol to needles of Δ^4-25D-*spirostene*-1β,2β,3α-*triol* 1,2-*acetonide* 3-*acetate* (XVIIIb), m.p. 212–214°, $[\alpha]_D$ +21° (*c* 1·04, chloroform). (Found: C, 72·89; H, 9·27. $C_{32}H_{48}O_6$ requires: C, 72·69; H, 9·15%).

This XVIIIb (60 mg) was saponified with 1% methanolic KOH solution (5 ml) under reflux for 1 hr. Recrystallization of the product from methanol gave needles of XVIIIa, m.p. 227–230° (Found: C, 74·06; H, 9·54. $C_{30}H_{46}O_5$ requires: 74·03; H, 9·53%). This was identical with the above-mentioned sample of XVIIIa in all respects.

Oxidation of Δ^4-25D-*spirostene*-1β,2β,3α-*triol* 1,2-*acetonide* (XVIIIa) *with manganese dioxide*

To a solution of the foregoing XVIIIa (37 mg) in chloroform (4 ml) was added manganese dioxide (0·3 g) and the slurry was stirred for 2·5 hr at room temp. After working up in the usual manner it yielded Δ^4-25D-spirostene-1β,2β-diol-3-one acetonide (VI)[2], as needles from methanol, m.p. 205–208°.

Tetrahedron, 1960, Vol. 10, pp. 12 to 25. Pergamon Press Ltd. Printed in Northern Ireland

PREPARATION OF DERIVATIVES OF AMIDINEUREA AND THEIR REACTIONS

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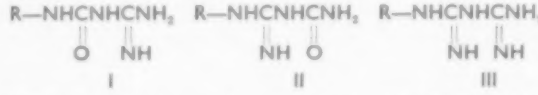
(*Received* 3 *December* 1959)

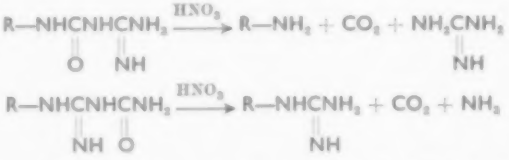
Abstract—A new method for preparing 1-amidine-3-arylureas or-3-alkylureas (I) from aryl or alkyl amine and cyanoguanidine or by hydrolysis of corresponding aryl or alkyl biguanides is described. The reaction of salts of amidineureas with primary or secondary amines to yield substituted ureas is described.

Aromatic amidineureas

MONOSUBSTITUTED aromatic derivatives of amidineureas can exist in two isomeric forms, viz. as 1-aryl-3-amidineureas (I) and 1-arylamidineureas (II).



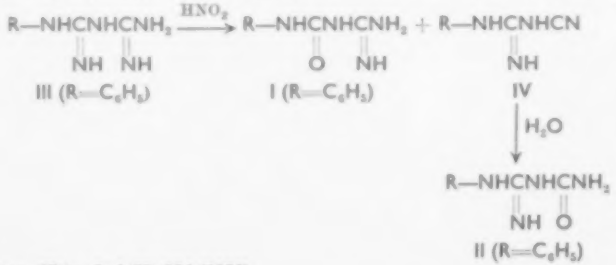
The isomers differ in behaviour when warmed with dilute nitric acid,[1] according to the equations:



Another reaction characterizing derivatives II is the formation of complex compounds with metals such as Cu, Ni. 1-Aryl-3-amidineureas (I) do not form such complexes.

The difference between the infra-red spectra of 1-phenyl-3-amidineurea and 1-phenylamidineurea, the simplest representatives of I and II respectively, indicate a new method (described later) to distinguish these isomers.

Unlike the compounds II, the 1-aryl-3-amidineureas (I) are little known. 1-Phenyl-3-amidineurea (I, R = C_6H_5) and some of its derivatives, were first prepared by Pellizzari.[1] In the course of the reaction phenylcyanguanidine (IV) was also formed. The latter is readily hydrolysed to 1-phenylamidineurea. (II, R = C_6H_5).

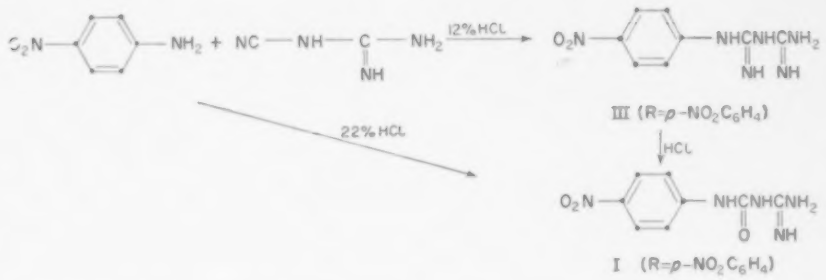


[1] G. Pellizzari, *Gazz. Chim. Ital.* **53**, 384 (1923).

Amidineureas and some aromatic derivatives (I) have also been prepared by Passerini[2], Junod[3] and Kundu and Ray[4].

A good yield of 1-amidine-3-*p*-nitrophenyl-urea (I, R = *p*-$NO_2C_6H_4$) is obtained when *p*-nitraniline reacts with cyanguanidine in a 22 per cent concentration of hydrochloric acid.[5,6]

p-Nitrophenylbiguanide (III, R = *p*-$NO_2C_6H_4$) is formed[7] when the concentration of hydrochloric acid is lower (12 per cent), but it is transformed into 1-amidine-3-*p*-nitrophenyl-urea (I, R = *p*-$NO_2C_6H_4$) by hydrolysis with 22 per cent hydrochloric acid.



This hydrolysis of biguanide derivatives (III, R = *p*-$CH_3CONHC_6H_4$) with hydrochloric acid was formerly observed by Mingoia and Ferreira,[8] but they ascribed the arylamidineurea structure (II, R = *p*-$NH_2C_6H_4$) to the product.

Starting from *p*-sulphamidephenylbiguanide in acid medium Kundu[9] obtained a compound which does not yield a complex with Cu and Ni and on this basis ascribed the structure I,(R = *p*-$NH_2SO_2C_6H_4$) to it. The structure was confirmed later by synthesis.

The correct structure for the product prepared by Mingoia and Ferreira[8] is I,(R = *p*-$NH_2C_6H_4$) as it is identical with that prepared by reduction of 1-amidine-3-*p*-nitrophenyl-urea.[10] (I, R = *p*-$NO_2C_6H_4$).

Further experiments have shown that (A) amines and cyanoguanidine in the presence of excess acid and (B) the hydrolysis of arylbiguanides (III) can be used to prepare compounds I.

Starting from a number of aromatic amines both reactions (A) and (B) have been carried out.[5,6,10–12] Generally speaking, a better yield of amidineureas (I) can be obtained by hydrolysing biguanides (III) according to (B). In some instances, however, the method (A) being simpler is advised. This applies to such amines as aniline, *p*-nitroaniline and *p*-aminobenzoic acid, which give yields of 80–90 per cent.

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[5] T. Urbański, B. Skowrońska-Serafinowa and H. Dabrowska, *Roczn. Chem.* **27**, 65 (1953).
[6] T. Urbański, B. Skowrońska-Serafin, H. Dabrowska and J. Jankowska, *Bull. Acad. Pol. Sci.* Cl. III, **1**, 74 (1953).
[7] F. H. S. Curd and F. L. Rose, *J. Chem. Soc.* **365** (1946).
[8] Q. Mingoia and P. C. Ferreira, *An. Fac. Farm. Odontol. Univ. Sao Paulo* **7**, 43 (1949); *Chem. Abstr.* **45**, 1971 (1951).
[9] N. Kundu, *Sci. & Cult.* **15**, 449 (1950); *Chem. Abstr.* **44**, 9367 (1950).
[10] T. Urbański, B. Skowrońska-Serafin and H. Dabrowska, *Roczn. Chem.* **28**, 423 (1954).
[11] T. Urbański, B. Skowrońska-Serafin and H. Dabrowska, *Bull. Acad. Pol. Sci.* Cl. III, **2**, 453 (1954).
[12] T. Urbański, B. Skowrońska-Serafin and H. Dabrowska, *Roczn. Chem.* **29**, 450 (1955).

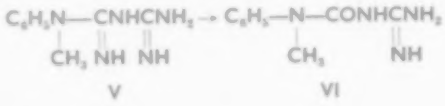
The preparation of amidineureas (I) from *m*- and *p*-aminophenols and *p*-chloroaniline was unsuccessful. Also the yield of I when using arylbiguanides prepared from some amines (III, R = *m*- and *p*-OHC_6H_4, β-naphthyl) is relatively low. This is probably due to instability of these amidineureas on warming with acids.

Table 1 gives the yields of arylamidineureas (I) prepared by reactions (A) and (B).

TABLE 1

R-NHCONHCNH₂ (NH) R	Yield of the reactions A	B
C_6H_5	83%	65%
p-$NO_2C_6H_4$	90%	90%
p-$COOHC_6H_4$	82%	95%
p-ClC_6H_4	—	65%
p-BrC_6H_4	20%	70%
p-$SO_3HC_6H_4$	—	50%
p-$NH_2SO_2C_6H_4$	20%	60%
p-$NH_2C_6H_4$	—	80%[a]
p-OHC_6H_4	—	10%
m-OHC_6H_4	—	14%
β-naphthyl	—	20%

Similarily, when 1-phenyl-1-methylbiguanide (V) was hydrolysed with hydrochloric acid, 1-phenyl-1-methyl-3-amidineurea (VI) resulted.[13]



V VI

Infra-red absorption spectra

Infra-red absorption spectra of four derivatives of 1-aryl-3-amidineurea (I, R = C_6H_5, hydrochloride; R = *p*-HO—C_6H_4, sulphate; R = *m*-HO—C_6H_4, sulphate; R = *p*-$NH_2SO_2C_6H_4$, hydrochloride) and the isomeric 1-phenylamidineurea (II, R = C_6H_5, hydrochloride) were examined in a Nujol mull, the ratio of substance/Nujol being 1 : 1. Infra-red spectrophotometer Hilger H–800 with sodium chloride prism was used.

The results are shown on Figs. 1–5 and the main frequencies are given in Table 2.

An exact assignment of some frequencies of derivatives of urea is complicated by the enolization and possible existence of a few polar forms of urea. In the region 1200–1000 cm^{-1} mono- and 1,4-disubstituted derivatives of benzene give frequencies which coincide with those of the $-NH_2$ group attached to an aliphatic chain.

All examined compounds give frequencies in the region 3500–3300 cm^{-1}. They are formed by NH_2 and phenolic groups (the latter in the compounds I, R = *p*- and *m*-HO·C_6H_4) bonded by intermolecular hydrogen bonds. The structure I (Figs. 1–4) gives a strong absorption in the region 1695–1680 cm^{-1}, typical for a group C=O in

[13] T. Urbański, B. Skowrońska-Serafin, A. Matusiak, A. Tyczyński and M. Zarukiewicz, *Roczn. Chem.* In press.

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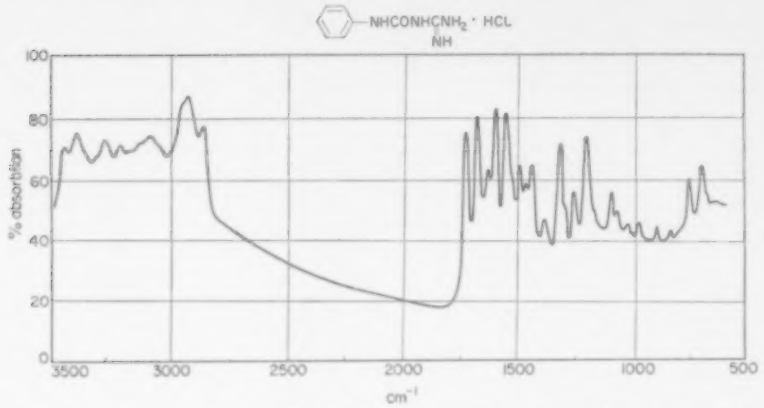


FIG. 1. Infra-red spectrum of 1-phenyl-3-amidineurea hydrochloride (I, R = C_6H_5).

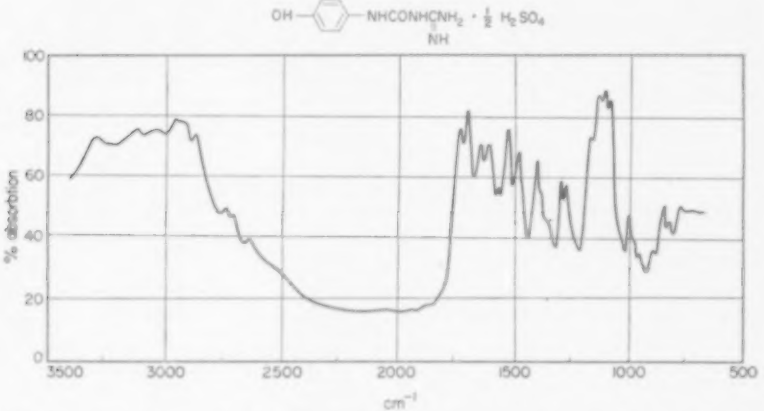


FIG. 2. Infra-red spectrum of 1-(*p*-hydroxyphenyl)-3-amidineurea-sulphate (I, R = *p*-OHC_6H_4).

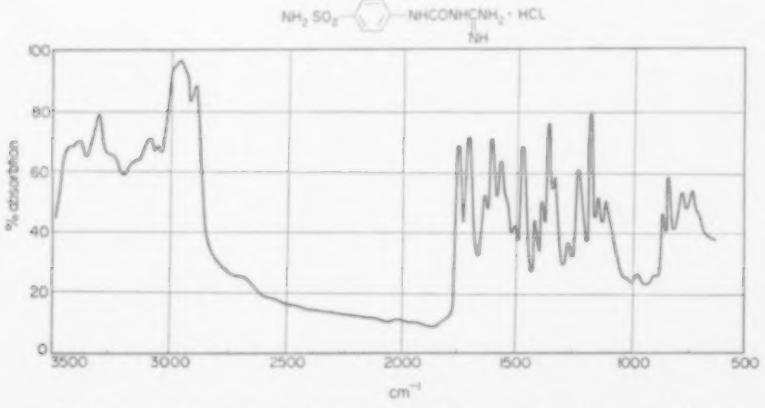


FIG. 3. Infra-red spectrum of 1-(*p*-sulphamidophenyl)-3-amidineurea sulphate (I, R = *p*-$SO_2NH_2C_6H_4$).

N-substituted amides. The analogous absorption band of the isomer II, ($R = C_6H_5$, Fig. 5) has apparently the maximum 1660 cm^{-1}, i.e. of a clearly lower frequency.

All the compounds show in addition two strong bands 1728–1715 cm^{-1} and 1620–1600 cm^{-1} which most likely are due to the groups C=O and C=NH. Boivin *et al.*[14]

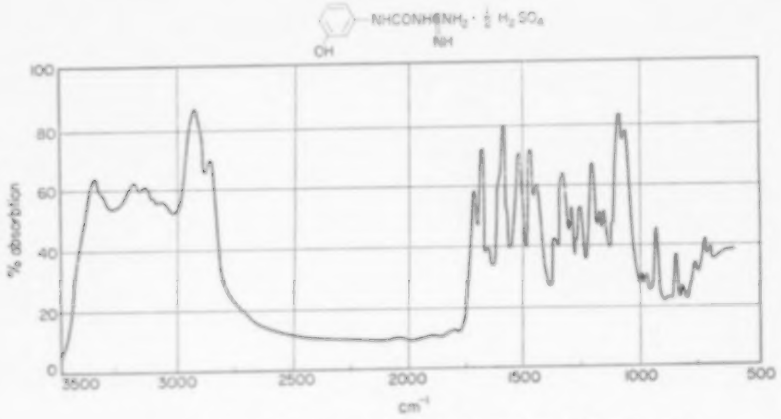


Fig. 4. Infra-red spectrum of 1-(*m*-hydroxyphenyl)-3-amidineurea sulphate (I, R = *m*-OHC_6H_4).

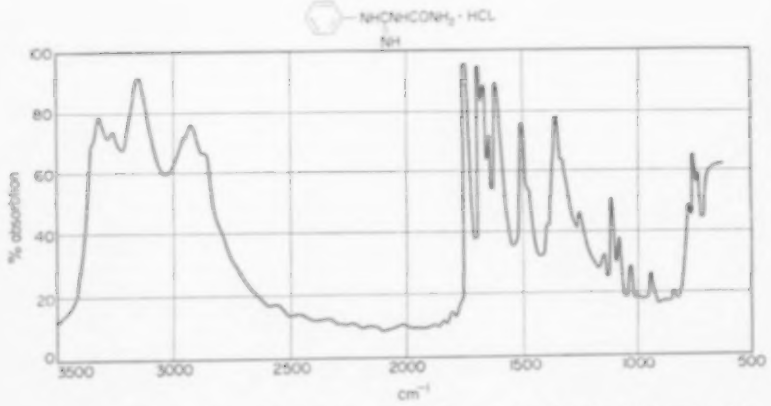


Fig. 5. Infra-red spectrum of 1-phenylamidineurea hydrochloride (II, R = C_6H_5).

assigned the bands 1710–1670 cm^{-1} to C=NH vibrations in some aromatic amidineurea nitrates. The isomer II, ($R = C_6H_5$) also gives a strong band at 1636 cm^{-1} which may be assigned to deformation vibrations of NH_2 in ureas,[15] and which is in agreement with the formula II.

Although it is difficult to draw a conclusion based on examination of only one substance (II), the marked difference between the absorption spectra of the compounds

[14] P. Boivin, W. Brigeo and J. Boivin, *J. Canad. Chem.* **32**, 242 (1954).
[15] H. M. Randall, R. G. Fowler, N. Fuson and J. R. Dangl, *Infra-red Determination of Organic Structures*. Van Nostrand, New York (1949).

I ($R = C_6H_5$) and II ($R = C_6H_5$) may give new evidence for the different structures of these compounds.

Boivin *et al.*[14] found bands 1380–1310 cm^{-1} in the examined nitrates of amidineureas, assigning them to the N=O bands in the nitrate ions, but we found the same frequencies (1374–1320 cm^{-1}) in the hydrochlorides and sulphates. These bands are

TABLE 2. INFRA-RED FREQUENCIES

I Ar-NHCONHC(=NH)—NH_2·HX					II
Ar	C_6H_5	*p*-OHC_6H_4	*p*-$SO_2NH_2C_6H_4$	*m*-HOC_6H_4	$C_6H_5NHCNHCONH_2$·HCl (=NH)
HX	HCl	$\frac{1}{2}H_2SO_4$	HCl	$\frac{1}{2}H_2SO_4$	
Fig.	1	2	3	4	5
	3465 s	3300 s	3425 s	3425 s	3310 s
	3410 s	3113 s	3370 s	3194 s	3250 s
	3290 s	1715 s	3290 s	1724 s	3135 s
	3219 s	1684 s	3068 s	1695 s	1720 s
	3095 s	1625 s	1725 s	1660 w	1660 s
	1728 s	1590 s	1688 s	1618 m	1636 s
	1680 s	1535 m	1614 s	1540 s	1620 s
	1620 m	1512 s	1580 s	1495 s	1590 s
	1595 s	1450 s	1550 s	1453 s	1563 m
	1555 s	1374 s	1495 w	1370 w	1545 w
	1500 m	1335 w	1454 s	1338 s	1480 s
	1460 m	1270 w	1400 m	1314 m	1453 m
	1445 m	1250 m	1373 m	1287 w	1375 w
	1377 w	1235 m	1339 s	1266 m	1332 s
	1320 s	1140 s	1320 s	1212 s	1313 s
	1260 m	1105 s	1263 w	1180 m	1233 m
	1210 s	1185 s	1205 s	1158 m	1140 w
	1118 m	1060 s	1161 s	1085 s	1100 m
	980 w	978 w	1125 m	1065 s	1074 m
	905 w	932 w	1092 m	1000 w	1028 w
	838 w	872 w	1008 w	976 w	1006 w
	763 m	825 m	970 w	945 m	945 w
	714 s	807 w	890 w	885 w	838 w
		755 w	843 m	852 m	760 m
			880 s	820 w	750 s
			770 m	775 w	730 m
				730 m	
				710 m	

more likely due to the stretching vibrations of a C—N band in secondary amines of the general structure Ar-NH—R[16] present in both I and II.

It is difficult to find more detailed assignment of the bands as the number of urea derivatives described in the literature and examined is very small. Examination of

[16] R. B. Barnes, R. C. Gore, U. Lidell and V. Z. Williams, *Infra-red Spectroscopy*. New York (1944).

infra-red absorption spectra of a larger number of urea and guanidine derivatives is being continued.

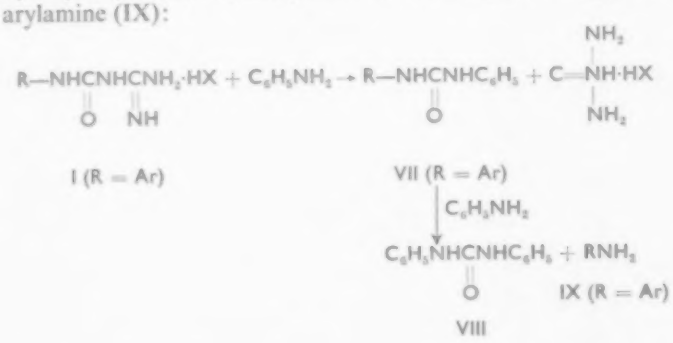
Aliphatic amidineureas

Preliminary experiments on the preparation of aliphatic amidineureas (I) by analogous reactions (A) and (B) have been carried out using benzylamine and n-butylamine.[13] In both cases we failed to obtain I directly from amines and cyanoguanidine according to the method (A). Aliphatic amines do not readily react with cyanoguanidine and thus, alkylbiguanides (III) are not prepared in aqueous solution, but require fusion of amine salts with cyanoguanidine. Also, hydrolysis of biguanides (III) to yield I (reaction B) occurred with a small yield in both cases. Benzylbiguanide (III, R = $C_6H_5CH_2$), yielded 11 per cent 1-amidine-3-benzylurea (I, R = $C_6H_5CH_2$) when hydrolysed with hydrochloric acid. In addition a number of decomposition products (benzylamine, guanidine, CO_2 and NH_3) were formed and a small quantity of unchanged benzylbiguanide remained.

In the case of n-butylbiguanide the yield of 1-amidine-3-(n-butyl)-urea (I, R = n-C_4H_9) was still lower; when the time of heating was shorter and the concentration of hydrochloric acid lower, a considerable amount of unchanged biguanide was left. When the time was longer and the concentration of the acid larger, a complete decomposition into n-butylamine, guanidine, CO_2 and NH_3 was produced, most likely due to instability of butylamidineurea on heating with conc. hydrochloric acid.

Reaction of amidineureas (I) *with primary and secondary amines*

Salts of arylamidineureas readily react with excess aniline to yield in the first instance 1-aryl-3-phenylurea (VII) and guanidine. Prolonged boiling yields carbanilide (VIII) and arylamine (IX):

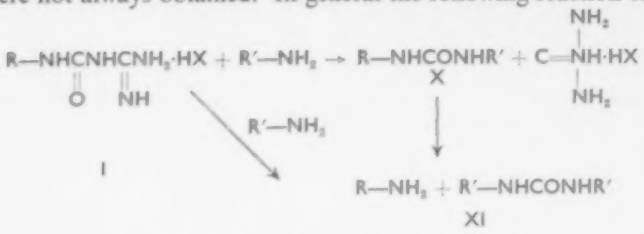


Very often the transformation of arylphenylureas into carbanilide was so fast that isolation of the intermediate (VII) was impossible.

The reaction of arylamidineureas with *o*-, *m*- and *p*-toluidine,[17] 2-aminopyridine,[18,19] cyclohexylamine, piperidine and n-butylamine[20] have been examined. In all these instances compounds of the type VII (R = $C_6H_4CH_3$ *o*-, *m*-, *p*-, 2-pirydyl, C_5H_{11}, piperidyl, n-C_4H_9) were formed, but symmetrical derivatives of urea of the

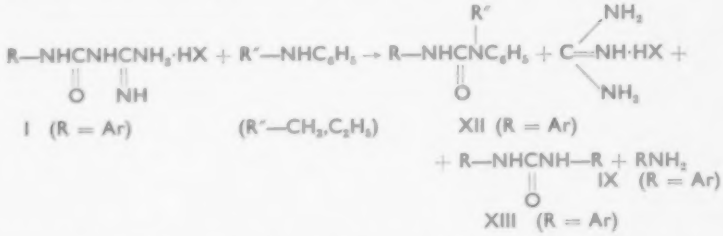
[17] T. Urbański, B. Skowrońska-Serafin and G. Chadzyński, *Roczn. Chem.* In press.
[18] T. Urbański and B. Skowrońska-Serafin, *Bull. Acad. Pol. Sci.* Cl. III, **4**, 361 (1956).
[19] B. Skowrońska-Serafin and T. Urbański, *Roczn. Chem.* **30**, 1189 (1956).
[20] T. Urbański, B. Skowrońska-Serafin and J. Zyołwski, *Roczn. Chem.* In press.

type (XI) were not always obtained. In general the following reaction can be given:

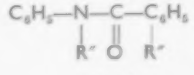


The reaction of salts of the arylamidineureas with amines is a convenient method of preparing disubstituted derivatives of urea of the general formula X. Table 3 gives the disubstituted ureas (X) and (XI) prepared by this method.

The reaction of salts of 1-aryl-3-amidineureas with secondary aromatic–aliphatic amines has a different trend.[17,19,21] When a salt of aryl amidineura (I, R = Ar) is warmed to boiling with N-methyl or N-ethyl-aniline, 1-aryl-1-alkyl-3-arylurea (XII) and a guanidine salt is obtained together with a small quantity of sym-diarylurea (XIII). Prolonged boiling reduces the yield of XII, increases the yield of XIII and arylamine, and produces tarry decomposition products.



The reaction differs from that with primary amines in that the sym-diarylurea (XIII) contains the same R-groups as the original arylamidineurea and dialkylcarbanilide (XIV) which would be analogous to carbanilide (VIII) is not formed.



When XII is boiled with an excess of N-alkylarylamine, it is recovered unchanged after several hours.

Biological activity

All derivatives of guanidine described in this paper possess a pronounced biological activity and have been examined against TB, tumor cells and malaria.

Toxicity. Amidineureas (I) proved to be of relatively low toxicity,* the LD_{50} being, when taken per os 1–3 g/kg, and when applied intravenously 0·1 g/kg. Biguanides are of much higher toxicity, β-naphthylbiguanide[23] being LD_{50} per 0·1 g/kg.

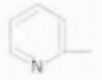
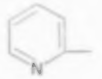
* These were examined by Dr. J. Venulet, Miss K. Jakimowska and Miss A. Urbańska.

[21] T. Urbański and B. Skowrońska-Serafin, *Bull. Acad. Pol. Sci.* Cl. III, **4**, 363 (1956).

[22] T. Urbański, B. Serafinowa, S. Malinowski, S. Ślopek, I. Kamieńska, J. Venulet and K. Jakimowska, *Gruźlica* **20**, 153, 293 (1952).

[23] T. Urbański, S. Malinowski, B. Skowrońska-Serafin, B. Chechelska, H. Dabrowska, J. Falecki, D. Gürne, S. Ślopek, I. Kamieńska, J. Venulet, K. Jakimowska and A. Urbańska, *Gruźlica* **22**, 681 (1954).

Table 3

I R—NHCONHCNH₂·HX (NH)	R′NH₂	X RNHCONHR′	XI R′NHCONHR′
R	R′	Yield %	Yield %
C_6H_5	C_6H_5	96	—
	o-$CH_3C_6H_4$	58	65
	m-$CH_3C_6H_4$	42	67
	p-$CH_3C_6H_4$	68	79
	n-C_4H_9	94	—
		75	75
		50	—
p-$NO_2C_6H_4$	C_6H_5	80	60
	n-C_4H_9	10	—
		95	80
		66	10
p-$COOHC_6H_4$	C_6H_5	60	98
p-$SO_3HC_6H_4$	C_6H_5	—	70
p-$NH_2SO_2C_6H_4$	C_6H_5	90	60
p-ClC_6H_4	C_6H_5	40	62
p-BrC_6H_4	C_6H_5	30	70
p-OHC_6H_4	C_6H_5	—	80
m-OHC_6H_4	C_6H_5	—	80
p-$NH_2C_6H_4$	C_6H_5	—	65
β-naphthyl	C_6H_5	51	80
	piperidine	94	—
		92	88
	n-C_4H_9	98	—
		20	—
$C_6H_5CH_2$	$C_6H_5CH_2$	90	—
	C_6H_5	75	30
n-C_4H_9	n-C_4H_9	90	—
	C_6H_5	50	30

Antituberculous activity. This was examined* *in vitro* by means of *Mycobacterium smegmatis* strains, Myc. 279 and $H_{37}Rv$. The most potent among amidineureas were compounds I. ($R = p\text{-}NO_2C_6H_4$;[22] $R = p\text{-}ClC_6H_4$;[23] $R = p\text{-}BrC_6H_4$.[24]) They were active against Mycobacteria at the concentration 1–5 mg %.

Among biguanides β-naphthylbiguanide[23] and *p*-nitrophenylbiguanide[24] were particularly active, their bacteriostatic concentration being 2 mg % and 8–15 mg % respectively.

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TABLE 4

Compounds	Kind of cells								
	Ehrlich ascites carcinoma			Amytal ascites sarcoma			Leucocytes of guinea pigs		
	concentration of compounds in μg/ml								
	1000	100	10	1000	100	10	1000	100	10
I $R—NHCONHCNH_2$ ‖ $NH\cdot HCl$ R									
$p\text{-}NO_2C_6H_4$	+++	+++	+++	+++	+++	+++	+++	+++	+++
C_6H_5	+++	+++	++	+++	+++	++	+++	+++	+
$p\text{-}BrC_6H_4$	+++	+++	++	+++	+++	++	+++	+++	+++
$p\text{-}NH_2C_6H_4$	—	—	—	—	—	—	+++	++	+
$m\text{-}OHC_6H_4$	—	—	—	—	—	—	+++	+++	++
Compounds III $R—NHCNHCNH_2$ ‖ ‖ $NH\ NH\cdot HCl$ R									
$p\text{-}CH_3C_6H_4$	—	—	—	—	—	—	+++	+++	+++
β-naphthyl	+++	+++	++	+++	+++	++	+++	+++	+++
$p\text{-}BrC_6H_4$	±	±	—	±	±	±	+++	++	++
$p\text{-}NO_2C_6H_4$	+++	++	+	+++	++	+	+++	+++	+++
Mercuric chloride	+++	+++	+++	+++	+++	+++	+++	+++	+++

All substances were ineffective *in vivo* against experimental TB in mice, rats and guinea pigs.*

Antineoplastic activity. Experiments *in vitro* were carried out by Ślopek and Mordarski using the modified Miyamura test with three types of tumor cells, namely, Ehrlich ascites carcinoma, amytal ascites sarcoma and leucocytes of guinea pig.[25]

Table 4 tabulates the result of these tests.

The experiments *in vivo* will be carried out.

* By Professor S. Ślopek and Dr. M. Janowiec.

[24] T. Urbański, C. Belżecki, B. Chechelska, B. Chylińska, H. Dabrowska, J. Falecki, D. Gürne, L. Halski, S. Malinowski, B. Serafinowa, J. Zylowski, S. Ślopek, I. Kamieńska, J. Venulet, M. Janowiec, K. Jakimowska, A. Urbańska and A. Kuzniecow *Gruźlica* **26**, 889 (1958).

[25] S. Ślopek, H. Mordarska, M. Mordarski, T. Urbański, Skowrońska-Serafin and H. Dabrowska, *Bull. Acad. Pol. Sci.* Cl. III, **6**, 355 (1958).

TABLE 5

Substrates						R—NHCONHC(NH)NH$_2$ I					
						Hydrochloride				Base	
R—NH$_2$		DCDA g	HCl (conc) ml	Water ml	Heating period	m.p.	Yield		Cryst. solvent	m.p.	Cryst. solvent
R	g						g	%			
p-$NO_2C_6H_4$	13·5	8·4	17·0	11·0	30 min	280–282 (dec.)	13·5	90	dil HCl	231–232°	alcohol
p-$COOHC_6H_4$	5·0	3·1	1·5[a]	71·5	15 min	247–248° [b]	8·0	82	dil H_2SO_4	198–200°	water
C_6H_5	6·5[c]	4·2	5·0	1·0	5 hr	163–164° [d]	9·3	83	dil HCl	—	—
p-$SO_2NH_2C_6H_4$	6·3[c]	2·4	—	15·0	1·5 hr	—	1·6	20	—	212–213°	water
p-BrC_6H_4	2·5	1·7	(1) 2·5 (2) 2·0	2·5 4·0	45 min[e] 30 min[f]	200°	1·0	20	dil HCl	171–172°	water

[a] Conc. H_2SO_4
[b] Sulphate
[c] Hydrochloride
[d] With 1 mole crystal water
[e] After heating the reaction mixture was made alkaline to pH 8
[f] After heating for 45 min 2·0 ml conc. HCl and 4 ml water were added and the mixture heated for further 30 min.

Antimalarial activity. Experiments with chicks infected with *Plasmodium gallinaceum** show the best results with the compound I(R = *p*-$NO_2C_6H_4$). A dose of 40 mg/kg kept the chicks free from parasites in the peripheral blood, and a dose of 20 mg/kg diminished greatly the peripheral parasites.[26]

TABLE 6

Substrates					R-NHCONHC(NH)NH_2 I					
RNHC(NH)NHC(NH)NH_2·HCl		HCl (conc) ml	Water ml	Heating period	Hydrochloride				Base	
R	g				m.p.	Yield		Cryst. solvent	m.p.	Cryst. solvent
						g	%			
p-$NO_2C_6H_4$	5·0	18·0	13·0	1 hr	—	4·5	90	—	231–232°[a]	alcohol
p-$COOHC_6H_4$	2·0[b]	40·0	40·0	2 hr	~ 350°	2·2	95	—	198–200°[c]	water
C_6H_5	3·0	3·3	4·7	1 hr	163–164°	2·0	65	dil HCl	—	—
p-$NH_2SO_2C_6H_4$	5·0	6·0	15·0	30 min	~ 220°	3·0	60	—	212–213°	water
p-ClC_6H_4	3·8	1·2	4·0	20 min	206–207°	2·4	65	water	143–144°	water
p-BrC_6H_4	3·0	1·7	4·2	45 min	—	1·5	70	water	171–172°[a]	water
p-$SO_3HC_6H_4$	7·5[b]	22·0	56·0	1 hr	—	3·2	50	—	267–269°	sat $NaHCO_3$
p-OHC_6H_4	5·0	1·2	3·8	1 hr	214–215°[a]	0·5	10	water	—	—
m-OHC_6H_4	5·0	1·2	3·8	1 hr	220–222°[a]	1·5	14	water	—	—
β-naphthyl	13·8	14·0	70·0	1·5 hr	279–281°	2·1	21	water	177–179°	dil alcohol
$C_6H_5CH_2$	3·6[f]	3·0	7·5	5 hr	167–168°[f]	0·4	11	water	142–144°	water
1-Phenyl-1-methyl-biguanid·HCl (V)	10·0	6·0	3·0	2 hr	237–238° (VI)	6·0	60	5%HCl		

[a] The precipitate was filtered, dissolved in water and made alkaline with dil NaOH
[b] Free base with 1 mole H_2O
[c] Hydrolysis of hydrochloride occurs on boiling with water
[d] The precipitate was filtered hot and recrystallized from sat $NaHCO_3$
[e] M.p. of sulphate ; after cooling the reaction mixture was filtered and the product recrystallized from dil H_2SO_4 with 1 H_2O
[f] *p*-Toluenosulphonate

EXPERIMENTAL

Preparation of arylamidineureas (I) *from amines and cyanoguanidine*

Example. *p*-Nitroaniline (13·8; 0·1 mole) were dissolved in 17 ml HCl and 11 ml water at 50°. Cyanoguanidine (8·4 g; 0·1 mole) was added and the mixture heated cautiously; a vigorous reaction gave a crystalline product. After refluxing for 30 min the mixture was chilled, filtered and the crystals were washed with 22% HCl and alcohol, to yield 13·5 g (90%) 1-(p-*nitrophenyl*)-3-*amidineurea hydrochloride*, m.p. 280–282° (decomp.)

The filtrate, concentrated and made alkaline with NaOH, yielded 5·8 g *p*-nitraniline. For other derivatives see Table 5.

Preparation of arylamidineureas (I) *from arylbiguanides* (III)

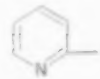
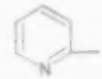
Example. Phenylbiguanide hydrochloride (3 g) were heated with 3·3 ml conc HCl for 1 hr. On cooling 1-*phenyl*-3-*amidineurea hydrochloride* precipitated; m.p. after recrystallization from dil HCl 163–164°, yield 2·0 g (65%). For other derivatives see Table 6.

Reaction of arylamidineureas (I) *with primary amines*

Example. 1-Phenyl-3-amidineurea hydrochloride (2·5 g) and 3 g *p*-toluidine were mixed and heated to a clear solution, and then refluxed gently for 1–2 min. After cooling dil HCl was added, the

* Carried out by Professor Yin-chiang Chin and Dr. Yun-yi Wu, Academy of Medical Sciences, Peking.
[26] Y. Ch. Chin, Y. Y. Wu, T. Urbański, B. Skowrońska-Serafin and J. Venulet, *Nature, Lond.* In press.

TABLE 7

Substrates				Heating period	R—NHCONH—R′	
R—NHCONHC(NH)NH₂·HCl		R′—NH₂			m.p.[a]	Yield %
R	g	R′	g			
C_6H_5	2·8	C_6H_5—	12·0	10 min	236–237°	96
	2·5	*o*-$CH_3C_6H_4$—	4·0	15 min	202–203°	58
	2·5	*m*-$CH_3C_6H_4$—	4·0	1–2 min	174–175°	42
	2·5	*p*-$CH_3C_6H_4$—	3·0	1–2 min	231–232°	68
	5·0	n-C_4H_9—	5·0	1 hr	130–131°	94
	5·0		5·0	2–3 min	182–183°	75
	5·0		5·0	2–3 min	189–190°	50
p-NO_2-C_6H_4	5·0	C_6H_5	15·0	1–3 min	218–219°	80
	10·0	n-C_4H_9	20·0	2 hr[b]	147–149°	traces
	5·0		10·0	2–3 min	205–207°	95
	1·0		2·0	1–2 min	242–247° subl.	66
p-COOH-C_6H_4	0·5	C_6H_5	10·0	10 min	300°	80
p-$NH_2SO_2C_6H_4$	1·0	C_6H_5	15·0	20 min	228–230°	90
p-Cl-C_6H_4	2·0	C_6H_5	10·0	1–2 min	237–238°	40
p-Br-C_6H_4	0·5	C_6H_5	3·0	1–2 min	243–245°	30
β-Naphthyl—	1·0	C_6H_5	5·0	1–2 min	237–238°	51
	5·0		10·0	20 min	204–205°	92
	5·0	n-C_4H_9	10·0	20 min	149–150°	98
	5·0		10·0	20 min	247–248°	20
	2·0		5·0	20 min	153–154°	94
$C_6H_5CH_2$	5·0[c]	$C_6H_5CH_2$	4·8	5 min	165–166	90
	5·0[c]	C_6H_5—	4·2	2 min	169–170°	75
n-C_4H_9—	5·0	n-C_4H_9—	5·0	1 hr	70–71°	95
	0·5	C_6H_5	1·0	1–2 min	129–130°	50

[a] After recrystallization
[b] Heating under presure 4·5 atm, 150–190°
[c] *p*-Toluenosulphonate

crude *1-phenyl-3-(p-tolyl)urea* was filtered off and recrystallized from anhydrous ethanol; m.p. 231–232°, yield 1·6 g (68%). For other derivatives see Table 7.

Prolonged heating of the same reagents or of X with an excess amine, resulted in formation of disubstituted ureas (XI). For yields and m.p. see Table 2.

TABLE 8

Substrates						Product		
$R-N(R')-CO-NH-C(=NH)-NH_2 \cdot HCl$			$R''-NH-C_6H_5$		Heating period	$RN(R')-CO-N(R'')-C_6H_5$		
R	R′	g	R″	g		m.p.	Yield g	Yield %
C_6H_5-	H—	3·0[a]	CH_3-	8·0	1–2 min	104–105°	1·8	65
		5·0	C_2H_5-	15·0	5 min	85–86°	2·8	50
p-$NO_2C_6H_4-$	H—	3·0	CH_3-	5·0	5–10 min	124–125°	0·8	26
		5·0	C_2H_5-	15·0	5 min	77–79°	1·5	35
p-ClC_6H_4-	H—	5·0	C_2H_5-	28·0	20 min	123–124°	1·6	30
C_6H_5-	CH_3	5·0	CH_3-	7·0	50 min	121–122°	2·0	38

[a] nitrate

Reaction of arylamidineureas with N-*methyl and* N-*ethyl-aniline*

Example. In an open flask N-methylaniline (1·2 g) and 1-phenyl-3-amidineurea nitrate (3 g) were heated as rapidly as possible (with an open flame) to obtain a clear solution. After cooling dil HCl was added, the precipitate extracted with benzene, dried with anhydrous Na_2SO_4, and evaporated to dryness. The crude product was recrystallized from alcohol to yield *1-methyl-carbanilide*, m.p. 104–105° (65%).

As an alternative procedure the precipitate formed after HCl acidification can be filtered, washed with H_2O, and recrystallized. For other derivatives see Table 8.

Acknowledgements—Our thanks are due to all our collaborators who took part in preparation of the compounds described in the present paper: Mrs. H. Dabrowska-Urbańska, Mr. J. Żylowski, Mr. G. Chadzyński, Mr. A. Matusiak, Mr. M. Zarukiewicz, Miss H. Wojciechowska and Mr. A. Tyczyński.

Our thanks are also due to Mrs. U. Dabrowska for carrying out the experiments with infra-red spectrophotometer and to Professor S. Ślopek, Dr. M. Mordarski, Dr. J. Venulet, Professor Yin-chiang Chin and Dr. Yun-yi Wu for carrying out the biological and pharmacological tests.

Tetrahedron, 1960, Vol 10, pp. 26 to 36. Pergamon Press Ltd. Printed in Northern Ireland

BENZOLOGUES AND OTHER DERIVATIVES OF PEROPYRENE

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Chemistry Department, The University, Glasgow

(*Received* 26 *January* 1960)

Abstract—Peropyrene (III) was synthesized via the diketone (II) and by reduction of peropyrenequinone (IV). The latter can also be obtained from the diketone (II). 4:4′-Dibenzanthronyl gave 4:4′-dibenzanthrenyl (V), the dehydrogenation of which yielded the yellow compound (VI) which displayed thermochomy involving the blue form (VIa). This decomposed to (VII). Condensation of benzanthrone with phosphorus oxychloride gave 4:5,11:12-dibenzoperopyrene (VIII), 4:5,9:10-dibenzoperopyrene (IX), 4:5,8:9-dibenzoperopyrene (X) and 2:3,8:9-dibenzoperopyrene (VII). 5:6,12:13-dibenzoperopyrene (XIV) was synthesized via (XII) and (XIII). A zinc dust melt of 8:8′-dibenzanthronyl (XVII) gave 3:4,11:12-dibenzobisanthene (XXI). A mixture of the dibenzanthronyls (XVII), (XVIII) and (XIX) gave 3:4,10:11-dibenzobisanthene (XX) in addition. The dinaphthoperopyrenes (XXIII) and (XXIV) resulted from a zinc dust melt of naphthanthrone (XXII).

WHEN perinaphthone (I) was reduced with aqueous sodium hydroxide solution and zinc dust a colourless product was obtained. It had no phenolic properties and its infra-red spectrum showed a strong carbonyl peak at 1675 cm^{-1}. Condensation of the

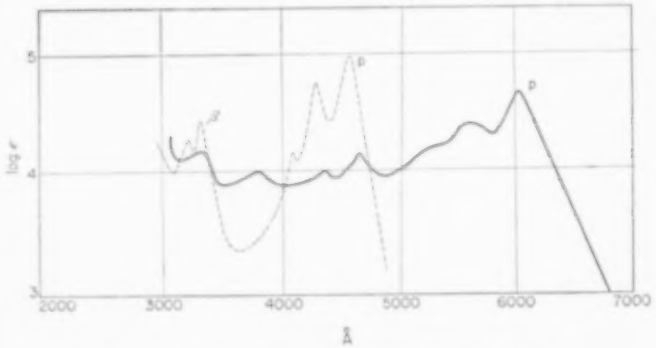


FIG. 1. Absorption max (Å) and log ε (in parentheses).
Peropyrene-3,8-quinone IV in 1,2,4-trichlorobenzene, 5980 (4·66), 5560 (4·48), 4650 (4·24), 4340 (4·11), 3800 (4·04), 3340 (4·20). Dichloroperopyrene in 1,2,4-trichlorobenzene, p: 4570 (4·92), 4280 (4·66), 4030 (4·18); β: 3300 (4·40).

diketone (II) with alcoholic potassium hydroxide gave peropyrene quinone (IV). This quinone was also obtained by condensation of perinaphthone (I) in alcoholic potassium hydroxide. It is described in the patent literature,[1] but has never been characterized as a pure compound. The absorption spectrum is shown in Fig. 1. It is obvious that the condensation of perinaphthone (I) proceeded in an analogous way to the condensation of benzanthrone to violanthrone.[2] A zinc chloride sodium chloride melt of the diketone (II) gave peropyrene (III). This hydrocarbon was also prepared

[1] Badische Anilin und Soda Fabrik, Ger. Pat. 283066 (1913).
[2] A. Lüttringhaus and H. Neresheimer, *Liebigs Ann.* **473**, 259 (1929).

in good yield by a zinc dust melt of peropyrene quinone. When the latter was oxidized with chromic acid, an acid was formed which yielded perylene on decarboxylation. This confirms the view that the carbonyl groups are located in the two terminal rings. The above syntheses gave much better yields than the one previously reported.[3] 4:4′-Dibenzanthronyl[2] was smoothly reduced to 4:4′-dibenzanthrenyl (V) with zinc dust, pyridine and acetic acid. For the absorption spectrum see Fig. 2. It could be dehydrogenated with chloranil, nitrobenzene or palladium charcoal in trichlorobenzene

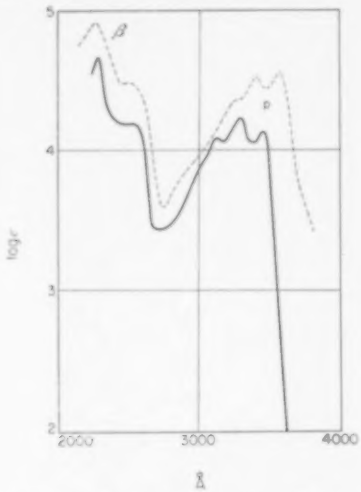


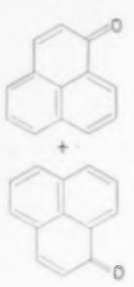
FIG. 2. Absorption max (Å) and log ε (in parentheses).
Benzanthrene in alcohol, p: 3440 (4·14), 3290 (4·22), 3120 (4·08); 2500 (4·20); β 2280 (4·64).
4:4′-Dibenzanthrenyl V in benzene, p: 3570 (4·54), 3410 (4·52); in alcohol, 2500 (4·50); β 2260 (4·90).

to a yellow compound, probably (VI), which when heated in xylene or nitrobenzene solution changed to a deep blue solution, showing an absorption band at 6000 Å. The colour disappeared again on cooling. The thermochromy could be observed many times in xylene solution before the compound was finally transformed into 1:2,9:10-dibenzoperopyrene (violanthrene, VII). This condensation also took place after a short boiling in nitrobenzene. Owing to its sensitivity, the compound (VI) could not be recrystallized in an analytical pure state. However, the assumption of the equilibrium (VI) $\rightleftharpoons$ (VIa) is the most likely explanation for the thermochromy.

When heated with benzene and aluminium chloride, peropyrene (III) gave a phenylperopyrene, which has an absorption spectrum closely related to peropyrene (Fig. 3). The phenyl group is most likely in one of the terminal rings because substitution in the positions 5 and 6 would have produced a new ring on cyclization and a corresponding major alteration in the spectrum. Peropyrene can be oxidized to peropyrenequinone which is identical with the quinone obtained by direct syntheses. Peropyrene does not form an adduct with boiling maleic anhydride and chloranil, but gives a little dichloroperopyrene (Fig. 1). It has therefore no perylene character. Unlike perylene the two central bonds cannot assume single bond character in terms of Kekule structures.[4] However, peropyrenequinone (IV) is a perylene derivative by

[3] E. Clar, *Ber. Dtsch. Chem. Ges.* **76**, 458 (1943).
[4] D. M. Donaldson, J. M. Robertson and J. G. White, *Proc. Roy. Soc.* A **220**, 311 (1953).

this definition. Accordingly, it forms quite readily an adduct with maleic anhydride, with or without chloranil. This brownish yellow anhydride could not be recrystallized from high boiling solvents because of the dissociation which also took place in an attempt to decarboxylate with soda lime or in quinoline with copper powder. Dissociation was also complete when the adduct was reduced with zinc dust in aqueous alkali. Violanthrone (1:2,9:10-dibenzoperopyrene-3,8-quinone) also gives a dissociable adduct.



I

II

III

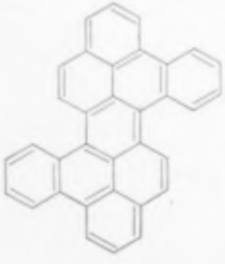
IV

V

VI

VI a

VII



VIII

IX

X

XI

A condensation of two molecules of benzanthrone with phosphorus oxychloride[5] gave besides the already known yellow 4:5,11:12-dibenzoperopyrene[6] two hitherto unknown dibenzopyrenes. They can have only the structure of a 1:2,6:7-dibenzoperopyrene (IX) and 1:2,11:12-dibenzopyrene (X). They are not identical with

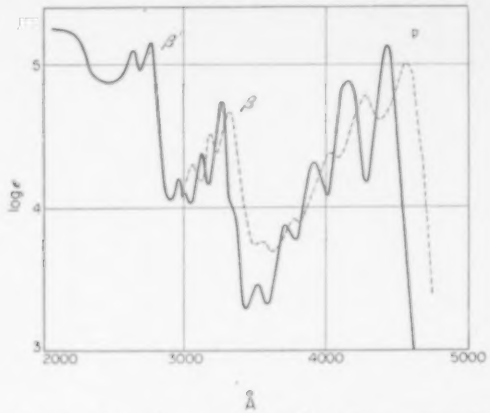


FIG. 3. Absorption max (Å) and log ε (in parentheses).
Peropyrene III in alcohol, p: 4365 (5·14), 4100 (4·90), 3860 (4·42), 3660 (3·94), 3480 (3·44); β: 3235 (4·74), 3090 (4·50), 2950 (4·24); β': 2770 (5·16), 2640 (5·10). Phenylperopyrene in benzene, p: 4530 (5·00), 4260 (4·80), 4030 (4·38); β: 3300 (4·68), 3160 (4·50).

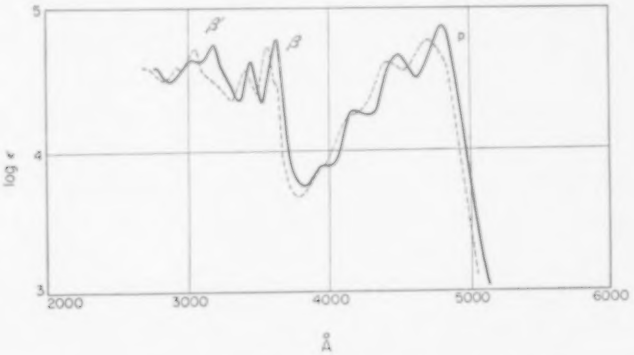


FIG. 4. Absorption max (Å) and log ε (in parentheses).
Dibenzoperopyrene m.p. 334–335, (IX or X) in benzene, p: 4820 (4·87), 4530 (4·66), 4200 (4·28), 3960 (3·89); β: 3630 (4·78), 3460 (4·60); β': 3185 (4·75), 3060 (4·63). Dibenzoperopyrene m.p. 279° (X or IX) in benzene, p: 4720 (4·78), 4450 (4·62), 4180 (4·27); β: 3580 (4·72), 3415 (4.55); β': 3070 (4·73), 2950 (4·59).

1:2,9:10-dibenzoperopyrene (violanthrene, VII). Their first absorption bands (Fig. 4) are located between the latter and 4:5,11:12-dibenzoperopyrene (VIII, Fig. 5) in accordance with the formulae (IX) and (X).

5:6,12:13-Dibenzoperopyrene (XIV, 2:3,8:9-dibenzcoronene) has been synthesized previously in a very complicated way involving numerous intermediate stages.[7] It could be more easily obtained from 1,4-dimethylanthraquinone which

[5] N. Campbell and A. A. Woodham, *J. Chem. Soc.* 843 (1952).
[6] E. Clar, Ger. Pat. 621861 (1933); *Ber. Dtch. Chem. Ges.* **76**, 458 (1943).
[7] R. Scholl and K. Meyer, *Ber. Dtsch. Chem. Ges.* **65**, 902 (1932).

yielded the diol (XII) when reacted with *o*-tolyl-lithium. Reduction with hydriodic acid in acetic acid gave the ditolylanthracene (XIII). Cyclodehydrogenation with palladium charcoal provided dibenzoperopyrene (XIV) in varying yields. Its absorption spectrum shows a striking resemblance with the deep red 1:2,8:9-dibenzoperopyrene (isoviolanthrene, (XI), Fig. 6) thus indicating that the two

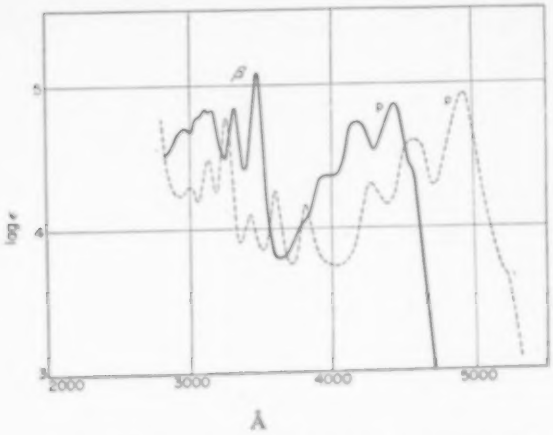


FIG. 5. Absorption max (Å) and log ε (in parentheses).
4:5,11:12-Dibenzoperopyrene VIII in benzene, p: 4450 (4·86), 4180 (4·73), 3980 (4·36); β: 3480 (5·10), 3320 (4·85), 3165 (4·82), 3110 (4·82), 2960 (4·70). 1:2,9:10-Dibenzoperopyrene (Violanthrene) VII in benzene, p: 4920 (4·91), 4580 (4·60), 4280 (4·28); β: 3820 (4·16), 3610 (4·26), 3430 (4·10); β': 3275 (4·76), 3140 (4·47), 3000 (4·30).

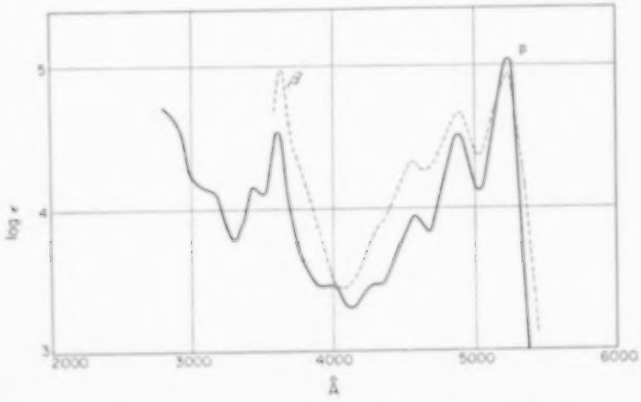


FIG. 6. Absorption max (Å) and log ε (in parentheses).
1:2,8:9-Dibenzoperopyrene XI in 1-methylnaphthalene, p: 5230 (4·90) 4880 (4·65), 4590 (4·34); β: 3640 (4·96). 5:6,12:13-Dibenzoperopyrene XIV in 1-methylnaphthalene, p: 5240 (5·02), 4880 (4·50), 4580 (3·94); β: 3620 (4·54), 3440 (4·16).

double bonds fused to peropyrene in the positions 5:6,12:13 have the same effect as two dienes fused to the positions 1:2,8:9.

3:4,11:12-Dibenzobisanthene (XXI) and 3:4,10:11-dibenzobisanthene (XX) cannot be obtained by a condensation of two molecules of benzanthrone. They were

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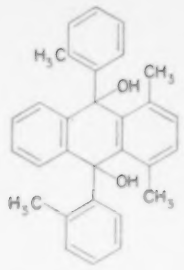
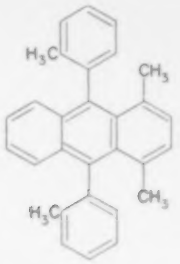
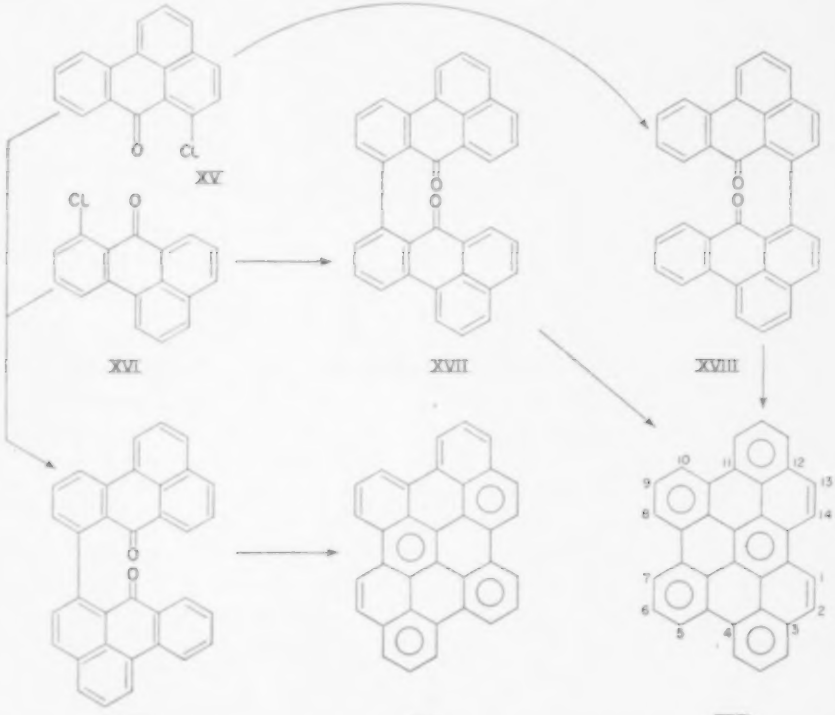


XII



XIII

XIV



XV XVI XVII XVIII XIX XX XXI

synthesized from 6- and 8-chlorobenzanthrone (XV) and (XVI) via the dibenzanthronyls. Pure 8:8′-dibenzanthronyl (XVII) was prepared from 8-chlorobenzanthrone with copper powder in nitrobenzene.[8] It gave the hitherto unknown pale yellow 3:4,11:12-dibenzobisanthene (XXI) in a zinc dust melt. It has 5 inherent aromatic sextets (marked with circles), i.e. more than any other hydrocarbon consisting of 2 benzanthrene complexes (except (VIII) which is non-planar) and therefore comes nearest to a fully benzenoid hydrocarbon like hexabenzocoronene.[9] Its p-bands (Fig. 7), accordingly, are the most shifted to the short wave part of the spectrum and it shows a red phosphorescence of long life in solid solution at low temperature.

[8] W. Bradley, *J. Chem. Soc.* 1622 (1948).
[9] E. Clar and C. T. Ironside, *Proc. Chem. Soc.* 150 (1958); E. Clar, C. T. Ironside and M. Zander, *J. Chem. Soc.* 142 (1959).

The isomer 3:4,10:11-dibenzobisanthene (XX) has only 4 inherent aromatic sextets. It is red and its p-bands are at longer wavelengths (Fig. 7) like the ones of (VII), (IX) and (X), whilst (XI) and (XIV) with only 3 inherent sextets have p-band at the longest wavelength (5150 Å in benzene). 3:4,10:11-dibenzobisanthene (XX) was prepared from a constant melting eutectic mixture of the two chlorobenzanthrones (XV) and (XVI), which, when treated with copper powder in nitrobenzene,

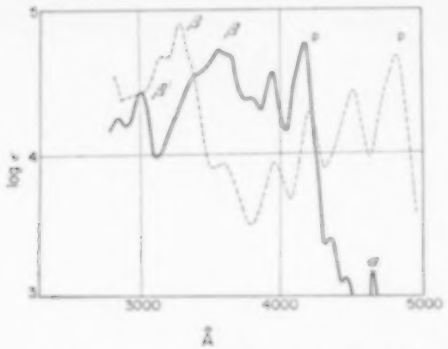
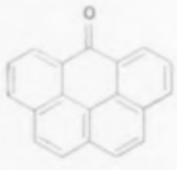


FIG. 7. Absorption max (Å) and log ε (in parentheses).
3:4,11:12-Dibenzobisanthene XXI in benzene, α: 4660 (3·20), 4475 (3·13), 4380 (3·39); p: 4170 (4·80), 3945 (4·58), 3810 (4·40); β: 3580 (4·73); β': 2995 (4·45), 2850 (4·25). 3:4,10:11-Dibenzobisanthene XX in benzene, p: 4820 (4·66), 4510 (4·40), 4200 (4·26), 3940 (3·90); 3580 (3·92); β: 3290 (4·92), 3160 (4·66), 3000 (4·40).

gave a mixture of the dibenzanthronyls (XVII), (XVIII) and (XIX). The zinc dust melt yielded a mixture of 3:4,11:12- and 3:4,10:11-dibenzobisanthene (XXI) and (XX) respectively. The former could be enriched in the mixture by chromatography, but not freed from (XXI). The spectrum of pure (XX) was obtained by the subtraction of the absorption curve of (XXI) from that of the mixture.

As could be expected by a comparison of the formulae (XX) and (XXI), the former reacted more readily with maleic anhydride and chloranil and its spectrum gradually disappeared from the mixture in the course of the reaction. However, (XXI) also appears to react to some extent because the decarboxylation of the resulting acids yielded an inseparable mixture of hydrocarbons.



XXII

XXIII

XXIV

Naphthanthrone (XXII) could be condensed like benzanthrone. This was done in fused zinc chloride with zinc dust. The main product of the reaction was a good

yield of dinaphtho-(7′:1′,1:13)(1″:7″,6:8)-peropyrene (XXIII). It was identical with the same hydrocarbon obtained by another synthesis.[10] An attempt to condense (XXIII) with bromomaleic anhydride yielded a dibromoderivative of (XXIII).

The chromatography of the reaction product yielded another isomer possibly (XXIV). Its absorption spectrum is recorded in Fig. 8. Although a spectroscopic examination of the crude condensation product indicated the presence of at least two

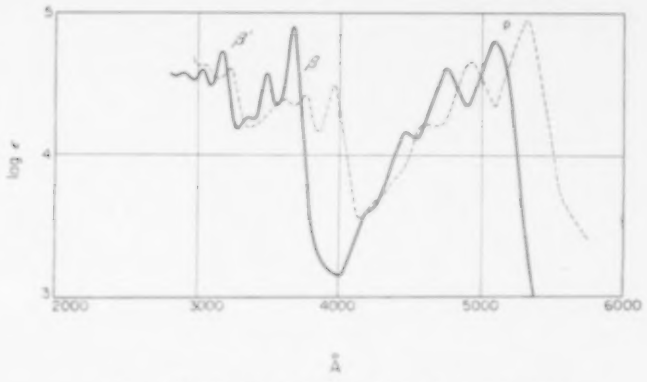


FIG. 8. Absorption max (Å) and log ε (in parentheses).
Dinaphtho-(7′:1′,1:13) (1″:7″,6:8)-peropyrene XXIII in benzene, p: 5100 (4·80), 4760 (4·59), 4470 (4·16); β: 3670 (4·92), 3490 (4·58), 3340 (4·26); β': 3170 (4·72), 3040 (4·61), 2900 (4·59).
Dinaphtho-(7′:1′,1:13) (1″:7″,9:11)-peropyrene XXIV in benzene, p: 5330 (4·93), 4950 (4·64), 4650 (4·20); β: 3960 (4·48), 3760 (4·42), 3630 (4·37); β': 3240 (4·60).

more isomers which could be expected in analogy with the condensation of benzanthrone, these hydrocarbons were not eluted from the chromatographic column even after a prolonged extraction.

EXPERIMENTAL*

7, 8, 7′, 8′-*Tetrahydro*-3, 3′-*diperinaphthonyl* (II). Perinaphthenone I (10 g) in hot xylene (50 ml) was added to a boiling mixture of sodium hydroxide (200 ml, 5%) and zinc dust (5 g). The solution became a deep red colour, which faded after 30 min. The xylene was removed by steam distillation and the zinc dust filtered off. Extraction with and the crystallization from xylene gave colourless needles of the *diketone* (II, 1·5 g) m.p. 256–257°. (Found: C, 86·1; H, 5·0 $C_{26}H_{16}O_2$ requires: C, 86·2; H, 4·9%).

Carbonyl peak: 1675 cm^{-1}. The colour in sulphuric acid was yellow.

Peropyrene-1,10-*quinone* (IV). Perinaphthenone (I, 10 g) was added slowly to a hot solution of potassium hydroxide (50 g) in methanol (100 ml) and the temperature raised to 150–160° for 5 min. The melt was digested with hot water, diluted to 1 l. and the air bubbled through the solution for several hours. The purple precipitate was filtered off and dried (9 g). A portion was crystallized from nitrobenzene, giving a dark purple powder, m.p. above 450° (dec). (Found: C, 87·0; H, 4·0 $C_{26}H_{12}O_2$ requires; C, 87·6; H, 3·4%). The quinone forms a red vat with alkaline sodium dithionite solution. Absorption spectrum Fig 1. The colour in sulphuric acid was blue.

Peropyrene-1,10-*quinone* (IV) *from the diketone* (II). The diketone (II, 100 mg) was added to a solution of potassium hydroxide (10 g) in methanol (50 ml) and the temperature raised with constant stirring to 150–160°. The typically purple colour of the quinone (IV) developed immediately, and after dilution and oxidation with air the dark purple quinone was obtained (90 mg). The absorption

* Melting points are uncorrected and were taken in evacuated capillaries. Microanalyses by Mr. J. M. L. Cameron and his staff of this department.

[10] E. Clar, W. Kelly, J. Monteath Robertson and M. G. Rossmann, *J. Chem. Soc.* 3878 (1956).

spectrum was identical to that shown in Fig. 1. The colour in sulphuric acid was blue. The vat with alkaline sodium dithionite was red.

Degradation of peropyrene-1,10-*quinone* (IV) *to perylene*. The solution of the quinone (IV, 1 g) in conc sulphuric acid was poured into a solution of chromium trioxide (1·4 g) in water (100 ml). This suspension was boiled for 1 hr, the solid product filtered off, extracted with dil alkali and acidified. The resulting crude acid (200 mg) was heated with soda lime under nitrogen. A little of a yellow hydrocarbon sublimed from the mixture at 380–400°/0·1 mm. The absorption spectrum of this substance in benzene was identical to that of perylene.

Peropyrene (III) *from peropyrene*-1,10-*quinone* (IV). The quinone (IV, 10 g) was ground together with zinc dust (10 g) and sodium chloride (10 g). Zinc chloride (50 g) was added and after the addition of water (1 ml) the mixture was melted and the temp raised with constant stirring to 290–310°, for 5 min. Digestion with dil acetic acid, removal of the zinc dust with acid, and sublimation 350°/0·02 mm gave the golden-yellow platelets of peropyrene, (3 g). Absorption spectrum as shown in Fig. 3. The colour in sulphuric acid was blue.

Peropyrene (III) *from the diketone* (II). The diketone (II, 500 mg) was mixed with sodium chloride (1 g) and zinc chloride (5 g), the mixture heated with constant stirring to 300° for 5 min. After decomposition, with dil acid, the reaction product was sublimed at 350°/0·1 mm giving peropyrene (400 mg). When peropyrene was oxidized with selenium dioxide in nitrobenzene the resulting peropyrenequinone showed the same absorption bands as IV.

Reaction of peropyrene-1,10-*quinone with maleic anhydride*. The quinone (IV, 1 g) was ground with maleic anhydride (20 g) and chloranil (1 g). The mixture was heated, and the blue coloured solution turned dull red and then brown (30 min). After cooling, xylene (50 ml) was added and the crude adduct (1·4 g), filtered off. The blackish solid gave a red coloured alkaline solution which had an absorption band at 480 mμ (diffuse). The adduct was insoluble in benzene or xylene and solvents such as acetic anhydride, dimethyl formamide, trichlorobenzene etc. gave solutions on heating which showed absorption bands at 600 mμ, 555 mμ of the peropyrene quinone (IV). Dissociation to the quinone (IV) also occurred when the adduct was boiled in dil alkali (5–10%) in the presence of zinc dust. Attempts to decarboxylate the adduct by heating with soda lime gave no pure product. Heating in quinoline with copper powder gave purple solutions of the quinone (IV). The reactions described above also occurred when chloranil was omitted from the reaction mixture.

Reaction of violanthrone with maleic anhydride. When violanthrone was boiled with an excess of maleic anhydride an alkali soluble adduct was formed in good yield. The alkali solution of the adduct had an absorption band at 510 mμ. This adduct behaved in a similar way to that described above, dissociation to violanthrone occurring readily.

Phenylperopyrene. Peropyrene (500 mg) was suspended in dry benzene (100 ml) and powdered aluminium chloride (1 g) was added in portions. The mixture was heated on the water bath, the initial strong blue fluorescence changing to blood red. After decomposition in the usual manner, the yellow product (450 mg) was dissolved in xylene, and chromatographed over alumina. Fractions showing the bands at 453 mμ and 426 mμ were collected. Concentration gave yellow platlets (300 mg) of phenyl peropyrene, m.p. 310–312°, which sublimed at 300°/0·1 mm. (Found: C, 95·2, 95·3; H, 4·6, 4·4; $C_{32}H_{18}$ requires: C, 95·5; H, 4·5%). Absorption spectrum Fig. 3. The colour in sulphuric acid was blue.

Attempted cyclization of phenyl peropyrene. Phenylperopyrene (100 mg) was added to a melt of aluminium chloride (5 g) and sodium chloride (1 g) at 120°, and the temp raised to 140° for 5 min. A sample showed that the starting material bands at 453 mμ and 422 mμ were unchanged. The temp was then raised to 180–190° for 10 min, and the mixture decomposed. Sublimation at 320°/0·1 mm gave a mixture which showed a strong band at 444 mμ, that is of peropyrene, and a weaker one at 453 mμ, i.e. unchanged phenylperopyrene.

Dichloroperopyrene. This was the only product obtained from the reaction of peropyrene (III) with maleic anhydride and chloranil. Peropyrene (120 mg) was mixed with excess maleic anhydride (2 g) and chloranil (500 mg). The mixture was refluxed until the 444 mμ band of peropyrene (III) disappeared (1/2 hr) and was replaced by one at 452 mμ. Hot nitrobenzene (50 ml) was added and the dark coloured crude product filtered off and washed (112 mg). It was insoluble in alkali. Sublimation at 400°/0·1 mm, and recrystallization from trichlorobenzene gave orange red needles (5 mg) m.p. 406–409°. (Found: C, 79·0, H, 3·1; $C_{32}H_{12}Cl_2$ requires: C, 79·2, H, 3·5%). This

compound gave a positive Beilstein test for chlorine. Absorption spectrum Fig. 1. The colour in conc sulphuric acid was blue.

4:4′-*Dibenzanthrenyl* (V). 4:4′-Dibenzanthronyl[3] (5 g) and zinc dust (100 g) were refluxed in pyridine (500 ml). Dil acetic acid (80 %, 250 ml) was added over 4 hr and the mixture boiled for a further 4 hr. The initially pink coloured mixture was almost colourless at the end of the reduction period. The reaction product was filtered off, zinc dust destroyed with conc acid, washed with water and dil ammonia and dried (3 g). The yellowish product was crystallized from xylene under carbon dioxide. 4:4′-dibenzanthrenyl forms yellowish needles, m.p. 352–354° (dec). (Found: C, 94·3; H, 5·4 $C_{34}H_{22}$ requires: C, 94·8; H, 5·2%). Absorption spectrum Fig. 2.

Dehydrogenation of 4:4′-*dibenzanthrenyl* (V). When 4:4′-dibenzanthrenyl (V) was dissolved in xylene and chloranil added the solution turned yellowish green and became deep blue on boiling the mixture. The intense colour faded on cooling and a yellow compound (VI) crystallized out. The thermochromic colour change could be obtained many times before the solution lost its capacity for colourization on heating. Prolonged boiling (10–15 min) also destroyed the thermochromism, and the solution then showed the characteristically sharp bands of violanthrene (VII) at 4920, 4580, 4280 Å. Owing to its reactivity the hydrocarbon (VI) could not be obtained in analytical pure state. Dehydrogenation by heating 4:4′-dibenzanthrenyl in nitrobenzene also produced the reversible colour changes described above. When a trace of iodine was added to the nitrobenzene solution immediate conversion to violanthrene occurred.

1:2,11:12-*Dibenzoperopyrene* (X) *and* 1:2,6:7-*dibenzoperopyrene* (IX). Mesobenzanthrone was condensed using phosphorus oxychloride as described by Campbell and Woodham.[5] The product was ground up with copper powder and sublimed at 350/0·1 mm to remove any traces of halogen. The sublimate (5 g) was extracted with xylene. The first fraction was found to be 4:5,11:12-dibenzoperopyrene (VIII). Recrystallization from xylene and sublimation gave orange needles. (Found: C, 95·6; H, 4·6; calc for $C_{34}H_{18}$: C, 95·8; H, 4·2%). The absorption spectrum was identical to that described in the literature[6] Fig. 5, m.p. 343–345°, mixed m.p. with authentic sample 343–344°. The colour in sulphuric acid was blue. The next most soluble isomer was another *dibenzoperopyrene* X or IX. This was recrystallized and sublimed giving golden brown needles, m.p. 279°. The colour in conc sulphuric acid was blue. (Found: C, 95·8; H, 4·6 $C_{34}H_{18}$ requires: C, 95·8; H, 4·2%). Absorption spectrum Fig. 4. A third *dibenzoperopyrene* IX *or* X was the last isomer soluble in xylene. It was recrystallized and sublimed. (Found: C, 95·8; H, 4·2. $C_{34}H_{18}$ requires: C, 95·8; H, 4·2%). It crystallized from xylene in orange prisms, m.p. 334–335°. The colour in conc sulphuric acid was blue. Absorption spectrum Fig. 4. Violanthrene (VII, 1:2,9:10-dibenzoperopyrene) remained as an insoluble residue from the extraction. It was purified by repeated extraction with xylene and sublimation. The absorption spectrum and m.p. 480° confirmed the identification.

9,10-*Dihydro*-9,10-*dihydroxy*-1,4-*dimethyl*-9,10-*di*-o-*toluyl anthracene* (XII). *o*-Bromotoluene (87·5 g) was added slowly to strips of lithium metal (7 g) suspended in dry ether (250 ml) in an atmosphere of nitrogen. The reaction was started by heating the mixture gently, and the ether kept refluxing by the addition of more halide. The mixture was boiled for 2–3 hr and the ether replaced by benzene. 1,4-Dimethylanthraquinone (30 g) was added as a benzene slurry. The reaction mixture turned brick red initially and after refluxing under nitrogen (2–3 hr) became dark brown. Decomposition with ice and dil acetic acid followed by steam distillation, and extraction with alkaline sodium dithionite (3 times) to remove unreacted quinone, gave the crude *diol* (35 g), m.p. 234–236°. Recrystallization from benzene gave colourless needles, m.p. 244–246°. (Found: C, 86·0; H, 6·4; $C_{30}H_{28}O_2$ requires: C, 85·7; H, 6·7%). The colour in sulphuric acid was brownish red.

1,4-*Dimethyl*-9,10-*di*-o-*toluyl anthracene* (XIII). The diol XII (5 g) was added to a mixture of acetic acid (100 ml) and hydrogen iodide (55 %, 4 ml), and refluxed for 1 hr. The crude product (4 g) was sublimed at 180–200°/0·1 mm (3 g). Recrystallization from ethanol gave yellow needles, m.p. 170–172°. (Found: C, 93·3; H, 6·7; $C_{30}H_{26}$ requires: C, 93·1; H, 6·9%). The colour in sulphuric acid was brownish.

5:6,12:13-*Dibenzoperopyrene* (XIV). 1,4-Dimethyl-9,10-di-*o*-toluyl anthracene (XIII, 500 mg) was sublimed slowly in an air-free carbon dioxide current over lumps of 15 % palladium charcoal, held at 400°. The product from this reaction was mostly unchanged starting material. When this was removed with benzene, a purple deposit of the dibenzoperopyrene was seen which was crystallized from methylnaphthalene to give a small amount (2–3 mg) of long, thin, shining green needles. The colour and appearance of these crystals and solutions were as described in the literature, as were

the colour changes from blue to red in conc sulphuric acid. For the absorption spectrum see Fig. 6. The temp of 400° was shown to be the minimum necessary and at this temp the palladium charcoal catalyst quickly became deactivated.

3:4,11:12-*Dibenzobisanthene* (XXI). 8-Chlorobenzanthrone[11] (4·0 g, XVI) was refluxed for 4 hr in nitrobenzene (25 ml) with copper powder (4·0 g). The crude product was filtered off and recrystallized from dimethyl formamide. The resultant 8:8′-dibenzanthronyl[11] (XVII, 2·0 g) was reduced at 300° in a melt of zinc dust (6·0 g), sodium chloride (6·0 g), and zinc chloride (30 g). The melt was dissolved in hydrochloric acid. After washing the product was sublimed to give a yellow hydrocarbon, which was crystallized twice from trichlorobenzene (570 mg), m.p. 432–433° and then resublimed. (Found: C, 95·6; H, 4·1; $C_{34}H_{16}$ requires: C, 96·2; H, 4·10%).

3:4,11:12-*Dibenzobisanthene* (XXI) dissolves slowly in conc sulphuric acid to give a violet colour. Absorption spectrum Fig. 7.

3:4,10:11-*Dibenzobisanthene* (XX). The eutectic mixture of 6-, and 8-chloromesobenzanthrones[11] (50 g XV, XVI) was refluxed with copper powder (50 g) in nitrobenzene for 4 hr. The resultant mixed dibenzanthronyls, XVII, XVIII and XIX, (5·9 g) were reduced with zinc dust (15 g) sodium chloride (15 g), and zinc chloride (75 g) at 310 for 15 min. The product was purified by sublimation and crystallization but its spectrum showed it to be a mixture. Treatment with alumimium chloride caused no alteration in the spectrum. (Found: C, 96·0; H, 4·0 $C_{34}H_{16}$ requires: C, 96·2; H, 4·1%). The spectrum is thus one of isomeric dibenzobisanthenes and subtraction of the 3:4,11:12-dibenzo bisanthene spectrum (Fig. 7) from that of the mixture gave a spectrum (Fig. 7) which was ascribed to 3:4,10:11-*dibenzobisanthene* (XX). Attempts to separate the mixture by chromatography over alumina were not successful.

Condensation of naphtho-[2′:7′,1:8]-*anthrone* (XXII). Naphthanthrone (XXII, 5·0 g) was ground up with zinc dust (15·0 g), sodium chloride (30 g) and zinc chloride (150 g). The mixture was melted and kept at 330° for 5 min, with constant stirring. The colour changed from yellow to red and then to brownish red, and traces of a red sublimate were seen. There was no frothing, since this reduction was done in the absence of water, in order to cause bimolecular condensation. The product was washed in the usual manner, and byproducts of low molecular weight were removed by extraction with petroleum ether (60–80°). The crude product was extracted with xylene in a soxhlet; since crystallization from xylene gave poor separation, the mixture (11·9 g) was chromatographed on alumina. A large amount of dinaphtho-(7′:1′,1:13) (1″:7″,′)-peropyrene (XXIII, 3·55 g), identical with a sample prepared by Clar *et al.*[10] was first obtained. After some mixed material came a pure solution which afforded reddish brown crystals of *dinaphtho* (7′:1′,1:13) (1″:7″,9:11)-*peropyrene* (XXIV, 0·4 g), m.p. 358–360°. (Found: C, 96·3; H, 3·8. $C_{38}H_{18}$ requires: C, 96·2; H, 3·8%). This compound gave a dark green colour in conc sulphuric acid. The absorption spectrum is shown in Fig. 8.

[11] W. Bradley and G. V. Jadhav, *J. Chem. Soc.* 1749 (1948); E. de Barry Barnett and M. A. Matthews, *J. Chem. Soc.* 2549 (1923).

Tetrahedron, 1960, Vol. 10, pp. 37 to 40. Pergamon Press Ltd. Printed in Northern Ireland

TRIPTYCEN AUS DEHYDROBENZOL UND ANTHRACEN

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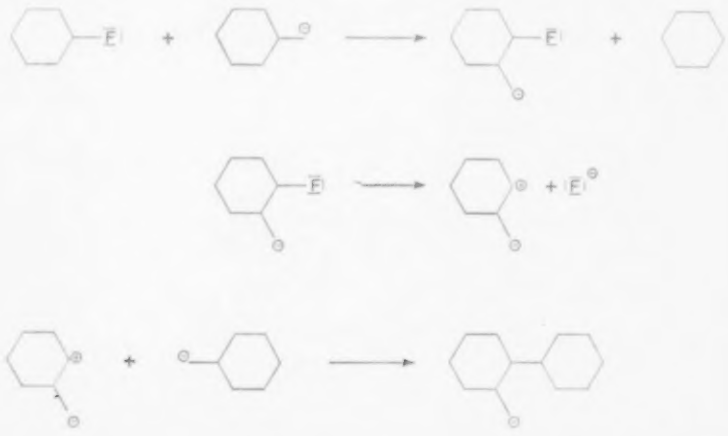
VOL. 10 1960

(*Received* 29 *January* 1960)

Abstract—Lithium hexaphenyl antimonide, $LiSb(C_6H_5)_6$, dissociates reversibly to a very small extent into pentaphenyl antimony and phenyl lithium. This equilibrium allows the use of phenyl lithium in extremely high dilution. By this means triptycen could be prepared in 23 per cent yield starting from the "at-complex", fluorobenzene and anthracene.

Zusammenfassung—Der nur geringfügige Zerfall des Lithium-hexaphenyl-antimonats zu Pentaphenylantimon und Phenyl-lithium im reversiblen Gleichgewicht gestattet es, Phenyl-lithium in minimaler Konzentration—gemäss dem Verdünnungsprinzip—einzusetzen. Unter diesen Bedingungen liess sich im "Eintopfverfahren" aus dem at-Komplex, Fluorbenzol und Anthracen Triptycen in 23 proz. Ausbeute gewinnen.

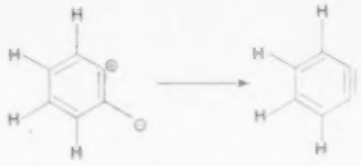
WITTIG[1] [*Naturwissenschaften* **30**, 697 (1942)] teilte mit: "Im anionisierten Fluorbenzol kann sich nun das Fluoranion mit seinem stabilen Oktett (zum Unterschied vom Methoxyl im Anisol) heteropolar ablösen und mit einem weiteren Molekül Phenyllithium das anionische Diphenyl bilden, das mit den vorhandenen Lithium-ionen *o*-Lithium-diphenyl liefert:



Und weiter S.700: "Das unterschiedliche Verhalten der aromatischen und olefinischen Halogenide (bei ihrer Anionisierung) dürfte darauf zurückzuführen sein, dass das intermediär entstehende Zwitterion $R—\overset{\oplus}{C}=\overset{\ominus}{C}—R$ in der olefinischen Reihe

[1] Dieses Zitat erscheint nicht überflüssig als Ergänzung zu den jüngst erschienenen Artikeln von R. Huisgen, *Theoretical Organic Chemistry, The Kekulé Symposium* S.158. London (1959) und von V. Franzen, *Chemiker-Ztg.* **1**, 3 (1960). Siehe auch G. Wittig, *Angew. Chem.* **66**, 11 (1954).

sofort zum Acetylenderivat stabilisiert wird, während das aromatische Zwitterion die entsprechende Unwandlung zum Dehydrobenzol:



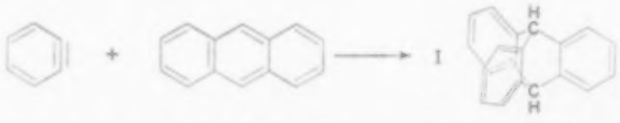
nicht vollziehen kann und den Ladungsausgleich auf anderem Wege sucht." Diese Überlegungen sind das Fazit von Untersuchungen, die seit 1938 mit einer Reihe von Mitarbeitern an metallierten Benzol- und Olefin-Derivaten durchgeführt und publiziert wurden.[2]

Nach dem damaligen Stand der Resultate wurde zwar das intermediäre Auftreten von Dehydrobenzol als *Zwitterion* postuliert, aber der Beweis für eine Symmetrisierung der dipolaren "Arinbildung" konnte nicht erbracht werden. Gewichtige, wenn auch in ihrer Beweiskraft nicht bindende Argumente zur Existenz kurzlebiger Dehydrobenzol-Moleküle fanden später in ausgezeichneten Arbeiten unabhängig voneinander Roberts und Huisgen.[3] Da die Operationen in Lösung durchgeführt wurden, konnte insbesondere eine Komplexbildung zwischen vorhandenen Neutralsalzen und Dehydrobenzol nicht ausgeschlossen werden.[4] Es erscheint daher notwendig, Dehydrobenzol als Gas—also im nackten Zustand—zu präparieren, worauf unsere im Gang befindlichen Untersuchungen abgestellt sind.

Auch die von Wittig und Mitarbeitern[5] nachgewiesenen Anlagerungen von Dehydrobenzol an cyclische und auch acyclische Diene[6] zu wohldefinierten Produkten wie z.B.:

erscheinen uns nicht streng beweisend für ein kurzlebiges Intermediärprodukt—sei es als dipolares oder seine beiden π-Elektronen schwach überlappendes Gebilde.[4]

Wir haben daher das dienophile Verhalten von Dehydrobenzol auf breiterer Basis studiert—in der Erwartung, hierbei auf einen eindeutigen Sachverhalt zu stossen. Im Zuge dieser Arbeiten gelang u.a. die Synthese des *Triptycens* (I),[7] das von Bartlett und Mitarbeitern[8] erstmalig auf anderem Wege synthetisiert worden war. Aus o-*Fluorbrombenzol* und Magnesium in Tetrahydrofuran in Anwesenheit von Anthracen erhielt man den Kohlenwasserstoff I in 28 proz. Ausbeute (bezogen auf *o*-Fluorbrombenzol):



[2] Erste Mitteilung von G. Wittig, U. Pockels u. H. Dröge, *Ber. Dtsch. Chem. Ges.* **71**, 1903 (1938).
[3] Zusammenfassender Artikel von E. F. Jenny, M. C. Caserio u. J. D. Roberts, *Experientia* **14**, 349 (1958).
[4] Vgl. G. Wittig u. H. Härle, *Liebigs Ann.* **623**, 27 (1959).
[5] Zusammenfassung von G. Wittig, *Angew. Chem.* **69**, 245 (1957).
[6] G. Wittig u. H. Dürr, unveröffentlicht.
[7] G. Wittig u. R. Ludwig, *Angew. Chem.* **68**, 40 (1956); *Organic Syntheses* Vol. 39, p. 75. McGraw-Hill, New York (1959).
[8] *J. Amer. Chem. Soc.* **64**, 2649 (1942).

Im Bestreben, das schwerer zugängliche *o*-Fluor-brombenzol durch *Fluorbenzol* zu ersetzen, da dieses nach unseren Untersuchungen[9] bei Einwirkung von Phenyl-lithium ebenfalls in einer eliminierenden Substitution in Dehydrobenzol übergeht, wurde ein positives Resultat erzielt, als man zu einer Tetrahydrofuran-Lösung von Anthracen und überschüssigem Fluorbenzol im Laufe von 7 Stunden eine dem Kohlenwasserstoff äquivalente Menge Butyl-lithium zuführte. Man isolierte I in einer Ausbeute von 10 Proz.[10]

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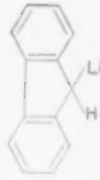
Dem hierbei angewandten Verdünnungsprinzip wird nun auch die folgende Variante gerecht. Wir hatten vor Jahren beobachtet,[11] dass metallorganische Komplexsalze eine unterschiedliche Stabilität besitzen, die durch ihr Zerfallsgleichgewicht:

$$[(C_6H_5)_nZ]Li \rightleftarrows (C_6H_5)_{n-1}Z + C_6H_5{\cdot}Li$$

gekennzeichnet ist. Ein Indizium für ihre Zerfallstendenz liefert u.a. das Verhalten der at-Komplexe[12] gegenüber Fluoren in Äther, das z.B. von Lithium-tetraphenyl-borat oder Lithium-triphenyl-beryllat überhaupt nicht angegriffen wird, während z.B. II im Laufe von 3 Tagen Fluoren in dass orangefarbene Metallierungsprodukt umwandelt:

II $\left[(C_6H_5)_3Cd\right]Li$ + Fluoren ⟶  + $(C_6H_5)_2Cd + C_6H_6$

das bei der nachfolgenden Carboxylierung 64 Proz. Diphenylenessigsäure bildete. Der gleiche Test auf die Beständigkeit des *Lithium-hexaphenyl-antimonats* (III)[13] führte zu dem Resultat, dass auch dieser isolierbare at-Komplex eine schwache Dissoziation in seine Addenden zeigt:

$$\text{III}\quad [(C_6H_5)_6Sb]Li \rightleftarrows (C_6H_5)_5Sb + C_6H_5{\cdot}Li$$

Eine ätherische Lösung von Fluoren nahm beim 15-stündigen Schütteln mit dem schwerlöslichen Antimonat III eine gelbe Farbe an, wonach durch Carboxylierung 12·5 Proz. Diphenylen-essigsäure erhalten wurden.

Da Pentaphenylantimon als Zerfallsprodukt Halogenbenzole nicht angreift, erschien III besonders geeignet, Phenyl-lithium in grosser Verdünnung zu liefern. Das ist in der Tat der Fall. Als man im "Eintopfverfahren" III mit Fluorbenzol und Anthracen in Tetrahydrofuran auf 100° erhitzte, konnte *Triptycen* (I) in 23 proz. Reinausbeute (bezogen auf den at-Komplex) isoliert werden. Es steht zu erwarten, dass sich die Ausbeuten namentlich bei Variation der at-Komplexe und der Solventien noch steigern lassen.

Das neue Prinzip, metallorganische Komplexsalze als Lieferanten für Phenyl-lithium in grosser Verdünnung einzusetzen, dürfte auch für andersartige Umsetzungen von Nutzen sein. Auch für die Kinetik der zum Dehydrobenzol führenden

[9] G. Wittig, G. Pieper u. G. Fuhrmann, *Ber. Dtsch. Chem. Ges.* **73**, 1193 (1940).
[10] G. Wittig u. E. Benz, *Angew. Chem.* **70**, 166 (1958).
[11] G. Wittig, F. J. Meyer u. G. Lange, *Liebigs Ann.* **571**, 171 (1951); G. Wittig, *Angew. Chem.* **62**, 231 (1950).
[12] Zur Definition der at-Komplexe s. G. Wittig, *Angew. Chem.* **70**, 67 (1958).
[13] G. Wittig u. K. Clauss, *Liebigs Ann.* **577**, 28 (1952).

eliminierenden Substitution wird es eine neue Basis schaffen, da die Möglichkeit gegeben ist, die Konzentration des metallorganischen Reagenzes—z.B. unter Pentaphenylantimon-Zusatz—nicht nur niedrig, sondern auch stationär zu halten.

EXPERIMENTELLER TEIL

Metallierung von Fluoren. 4 m Mol frisch bereitetes und mit Äther gewaschenes *Lithium-hexaphenyl-antimonat*[12] wurde nach dem Trocknen mit einer Lösung von 4 m Mol *Fluoren* in 70 cc absol. Äther überschichtet (alle Operationen unter Stickstoff) und 15 Stunden lang geschüttelt. Das gelb gewordene Reaktionsgut carboxylierte man durch Zugabe von Trockeneis, fügte nach etwa 10 Min. Wasser hinzu und extrahierte die ätherische Phase mit verd. Natronlauge. Die beim Ansäuern sich abscheidende *Diphenylen-essigsäure* wurde ausgeäthert und aus Ameisensäure umkristallisiert. Sie schmolz allein und auch in Mischung mit einem Vergleichspräparat bei 210° u. Zers.. Ausbeute 12·5% d.Th.

Triptycen. 3 g (5 m Mol) *Lithium-hexaphenyl-antimonat* wurden zusammen mit 15 g *Fluorbenzol* und 1·8 g (10 m Mol) *Anthracen* in 100 cc absol. Tetrahydrofuran unter Stickstoff 60 Stunden lang geschüttelt. Da sich die Menge des schwerlöslichen at-Komplexes nur wenig verringert zu haben schien, wurde nun der Ansatz unter gleichzeitigem Schütteln auf 80–100° erhitzt. Nach 2 Stunden war das Komplexsalz nahezu vollständig verschwunden.

Nach Zugabe von Methanol wurde die Lösung eingedampft und der Rückstand mit siedendem Wasser, dem etwas verd. Salzsäure zugefügt war, zweimal ausgezogen, getrocknet und mit 3 g *Maleinsäureanhydrid* in 30 cc Xylol 20 Min. gekocht. Das auskristallisierende Anthracen-Addukt wurde abgesaugt (2·2 g vom Schmp. 254–256°). Anschliessend kochte man die verbleibende Xylol-Lösung 2 Stunden mit 40 cc 2 N Natronlauge, trennte die Schichten und dampfte die Xylol-Lösung ein.

Beim Digerieren des anfallenden Produktes mit Tetrachlorkohlenstoff blieben 1·1 g *Triphenylstibinoxyd* vom Schmp. 205–209° ungelöst. Beim nachfolgenden Chromatographieren der Tetrachlorkohlenstoff-Lösung an 50 g Aluminiumoxyd (Merck, sauer) erhielt man neben 50 mg *Triphenylstibin* vom Schmp. 48–49° (Mischprobe) 0·4 g rohes *Triptycen*, das nach Umkristallisation aus Cyclohexan bei 252–254° schmolz (Mischprobe mit Vergleichspräparat). Ausbeute 0·29 g = 23% d.Th., bezogen auf den eingesetzten at-Komplex.

Tetrahedron, 1960, Vol. 10, pp. 41 to 44. Pergamon Press Ltd. Printed in Northern Ireland

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ON THE STABILITY OF SUBSTITUTED DIPHENYLENES

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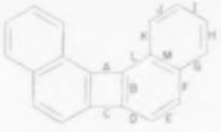
(*Received* 11 *March* 1960)

Abstract—Simple molecular-orbital calculations of the π electron energies and bond orders in the linear dibenzodiphenylene (I) and the *cis*-dibenzodiphenylene (II) are sufficient to show that the resonance energy of I exceeds that of II by about 4·3 kcal/mole. Similar conclusions follow from the bond orders in the central cyclobutadiene-like ring.

A NUMBER of derivatives of diphenylene(III) have been synthesized:[1,2] of these, 2:3,6:7 dibenzodiphenylene(I) and 1:2,7:8 dibenzodiphenylene(II) are of considerable interest because of the great difference they exhibit in their properties, as emphasized in a recent note by Curtiss.[3] I is very highmelting and exceedingly stable (unchanged on sublimation at 350°) whereas II decomposes easily and behaves as a highly unsaturated compound.

I



II

III

Both of these molecules are derived from diphenylene(III) by benzenoid annellation, but they may equally be regarded as derived from the hypothetical cyclobutadiene by annellation of naphthalene systems in the 2:3- and 1:2-positions respectively. The greater stability of I as compared with II must be related to the electron distribution in the region of this central cyclobutadiene-like ring. For cyclobutadiene[4] is not stable in a totally aromatic (i.e. square) configuration, and tends to distort in such a way as to favour a Kekule structure such as ⊓ or ⊔. It would follow from this that if the naphthalene regions in I and II took up the predominant Kekule bond diagrams, as shown in the figure, then in II we should have a situation in which the bonds labelled A and C would inevitably be weak, and where we might expect a lower stability than in I where none of the π-electron influences

[1] R. F. Curtiss and G. Viswanath, *J. Chem. Soc.* 1670 (1959).
[2] M. P. Cava and J. F. Stucker, *J. Amer. Chem. Soc.* 77, 6022 (1955).
[3] R. F. Curtiss, *J. Chem. Soc.* 3650 (1959).
[4] C. A. Coulson, *Chemical Society Symposia.* Special Publication No. 12, p. 85. Bristol (1958).

responsible for the instability of cyclobutadiene would arise. We might even argue that II had a locally pseudo-aromatic structure, using the terminology introduced by Craig,[5] and would therefore be expected to be unstable and unconjugated by analogy. Recently, Baker *et al.*[6] have shown that the chemical reactivity of diphenylene can be well understood in conjunction with simple molecular-orbital theory, if it is assumed that the most important contributing structure in diphenylene is that shown in III. Now the bond structures drawn in I and II are extreme, and no one suggests that the double-bonds are strictly localized in this way. But it should be possible to calculate the bond orders in I and II, and see whether the explanation which we have suggested for the difference between these molecules, is correct.

We have used the standard simple molecular-orbital theory, of Hückel type, with no inclusion of overlap integrals and with the assumption that all Coulomb (i.e. electronegativity) terms have the same value α. Since, however, our concern is with the differences in bond order, it is important to allow for variable resonance integrals β_{rs}. Without including some sort of dependence of β_{rs} on bond length, no self-consistence is possible. Lennard-Jones[7] used a Hooke-law potential function. But, partly through an inadequate knowledge of the way in which the radius of a carbon atom depends on the type of σ-hybridization, his predicted bond lengths were not entirely satisfactory. We have therefore preferred to use the functional form suggested by Longuet-Higgins and Salem[8] in their discussion of long cyclic and straight polyenes;

$$\beta(l) = -\mathrm{B}e^{-l/a} \tag{1}$$

where $a = 0{\cdot}3106$ Å, and $\beta(1{\cdot}40\ \text{Å}) = \beta_0 = -25{\cdot}56$ kcal/mole. Similarly, for the dependence of bond length l on π-bond order p, we used the linear relation

$$l = (1{\cdot}50 - 0{\cdot}15p)\ \text{Å}. \tag{2}$$

though recent studies on ethylene, where $p = 1$, suggest that the factor $0{\cdot}15p$ could more properly be replaced by $0{\cdot}16p$, and 1·51 is probably closer to the truth than 1·50. However, these are small points, which will not materially affect our conclusions. The forms (1) and (2) are such that the correct bond length and breathing-frequency are predicted for the case of benzene. Bond orders p are calculated according to the standard formula of Coulson.[9]

In order to obtain self-consistency, we want the calculated bond orders to lead, via (2) and (1), to molecular orbitals from which the original bond orders are now retrieved. This is achieved by an iterative procedure. First, we set all $\beta_{rs} = \beta_0$ and compute the molecular orbitals and bond orders p_{rs}. These lead to new β-values which must now be used to obtain improved bond orders, etc. The process is continued until further iterations make effectively no difference in computed bond orders and bond lengths. For I and III the starting values were available from the calculations of Crawford[10] and the Dictionary of Molecular Constants compiled by Coulson and Daudel. As might be expected, the effect of the various iterations is to

[5] D. P. Craig, *J. Chem. Soc.* 3175 (1951).
[6] W. Baker, J. F. W. McOmie, D. R. Preston and V. Rogers, *J. Chem. Soc.* 414 (1960).
[7] J. E. Lennard-Jones, *Proc. Roy. Soc.* A **158,** 280 (1937).
[8] H. C. Longuet-Higgins and L. Salem, *Proc. Roy. Soc.* A **251,** 172 (1959).
[9] C. A. Coulson, *Proc. Roy. Soc.* A **169,** 413 (1939).
[10] V. A. Crawford, *Canad. J. Chem.* 47 (1952); See also M. A. Silva and B. Pullman, *C. R. Acad. Sci., Paris* **242,** 1888 (1956).

increase the bond order of those bonds which are already fairly high, and to decrease those which are low. It is known, from much work on butadiene, that this improves the agreement with experiment.

Bond orders obtained for I, II and III by this self-consistent scheme are given in Table 1. The labelling of the bonds is as in the diagrams. Table 2 shows the total energies of I and II.

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TABLE 1. FINAL BOND ORDERS AND LENGTHS (Å)

Bond	Molecule I		Molecule II		Molecule III	
	π-Bond order	Length	π-Bond order	Length	π-Bond order	Length
A	0·273	1·459	0·205	1·469	0·219	1·467
B	0·472	1·429	0·655	1·402	0·572	1·414
C	0·757	1·387	0·171	1·474	0·701	1·395
D	0·506	1·424	0·631	1·405	0·612	1·408
E	0·557	1·416	0·688	1·397	0·705	1·394
F	0·733	1·390	0·581	1·413		
G	0·587	1·412	0·520	1·422		
H	0·548	1·418	0·763	1·386		
I			0·551	1·417		
J			0·764	1·385		
K			0·518	1·422		
L			0·579	1·413		
M			0·511	1·423		

TABLE 2. TOTAL π-ELECTRON ENERGIES

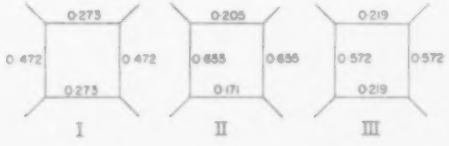
Molecule I	$20\alpha + 27{\cdot}307\beta_0$
Molecule II	$20\alpha + 27{\cdot}138\beta_0$
Difference	$0{\cdot}169\beta_0$

An indication of the rate of convergence of the calculated bond orders may be obtained by considering the highest and lowest bond orders in molecule I. These are bonds C and A respectively. Here successive integrations yield:

Bond C: 0·722, 0·750, 0·755, 0·757

Bond A: 0·316, 0·279, 0·274, 0·273

A glance at the tables shows that the central ring is described by the diagrams below:



Thus the degree of double-bond fixation increases in the sequence

Molecule I < Molecule III < Molecule II.

But this corresponds exactly with the sequence of stability of these molecules, the greater the degree of bond fixation, the less the extent of conjugation and the lower the stability. Another way of putting this is to notice that the extra benzenoid annellation of diphenylene lowers the bond orders of the two connecting bonds in II, but increases them in I. It is not surprising that the resonance energy of I exceeds that of II by $0{\cdot}169\beta_0 = 4{\cdot}3$ kcal/mole.

It is possible that the difference in stability may be greater than that arising from this difference in resonance energy. For, although the products of decomposition of II have not been described and we cannot therefore discuss any probable transition state, it seems very plausible that II would tend to split across bond C to give a di-α-naphthyl system, or across both A and C to give two separate naphthalenes. Now if we use the simple perturbation theory as developed by Coulson and Longuet-Higgins,[11] the energy required to break bond C in II is $0{\cdot}171 \times 2 \times$ corresponding resonance integral ($0{\cdot}788\ \beta_0$)

$$= 0{\cdot}269\beta_0.$$

The corresponding energy in I is $0{\cdot}237 \times 2 \times 0{\cdot}827\beta_0$

$$= 0{\cdot}451\beta_0.$$

The difference between these two is $0{\cdot}182\beta_0 = 4{\cdot}7$ kcal/mole. Alternatively, if we break both A and C in II and the corresponding bonds in I, the difference is $0{\cdot}903\beta_0 - 0{\cdot}598\beta_0 = 7{\cdot}8$ kcal/mole. Either of these values, in addition to the larger resonance energy of 4·3 kcal/mole possessed by I, is sufficient to account for the much greater observed stability of I as compared with II.

Acknowledgements—We would like to express our thanks to the Oxford University Computing Laboratory staff for help in obtaining the latent roots and vectors of the secular matrices arising in this problem on the Oxford Mercury Computer. One of us (M. A. A.) acknowledges the award of the Lytton Moslem scholarship from the Government of West Bengal, India.

[11] C. A. Coulson and H. C. Longuet-Higgins, *Proc. Roy. Soc.* A **191**, 39 (1947).

Tetrahedron, 1960, Vol. 10, pp. 45 to 54. Pergamon Press Ltd. Printed in Northern Ireland

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TERPENOIDS AND RELATED COMPOUNDS—I

CONSTITUENTS OF THE TRUNK BARK OF *MELIA AZADIRACHTA* LINN. AND THE STRUCTURE OF THE KETOPHENOL, NIMBIOL

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(*Received* 9 *March* 1960)

Abstract—From the trunk bark of *Melia azadirachta* Linn. have been isolated a branched chain paraffin alcohol, $C_{28}H_{54}O$, nimbosterol, sugiol (I, R = H) and a new ketophenol, nimbiol having the molecular formula, $C_{18}H_{24}O_2$. Nimbosterol has been identified as β-sitosterol and nimbiol has been shown to possess the structure (II, R = H). The biogenetic considerations for the possible formation of sugiol and nimbiol in the same plant have also been discussed.

Melia azadirachta Linn. syn. *Azadirachta indica* Juss (Sanskrit: Nimba) commonly known as "neem" or Indian Lilac is an evergreen tree, usually 40–50 ft in height, belonging to the Meliaceae family. The bark, leaves and fruits have been used in the Ayurvedic system of medicine from very ancient times and are mentioned in most of the ancient Sanskrit medicinal literatures like Susrutasanhita. So much is its popularity as a medicinal plant that almost every house in many parts of rural India has a neem tree in the compound. The bark is regarded as bitter, tonic, astringent and useful in fever, thirst, nausea, vomiting and skin diseases.[1] The earlier chemical work on the different parts of the tree are contradictory and inconclusive.[1] The systematic investigations on the tree were for the first time carried out by Siddiqui *et al.*[2a–g], who isolated besides the amorphous bitter principles, nimbidin and nimbidol, two crystalline bitter principles, nimbin and nimbinin, a nonacosane, a sterol named as nimbosterol, a flavone named as nimbicetin and a glucoside of nimbosterol named as nimbosterin. The flavonoid constituents of neem were identified by Pankajamani and Seshadri[3] and neem gum was investigated by Mukherjee and Srivastava.[4]

From the trunk bark of neem Siddiqui *et al.*[2e,f] isolated besides the amorphous bitter principle, nimbidin, the crystalline compounds, nimbin, nimbinin and nimbosterol. The method of these workers included the percolation of the bark with ethyl alcohol followed by the partition of the extract between petroleum ether and 80 per cent ethyl alcohol. The petroleum ether layer yielded nimbosterol, m.p. 137°. The ethanolic layer yielded nimbidin, nimbinin and nimbin. Because of the medicinal importance of the trunk bark, we undertook a systematic investigation of it and following a different method of extraction were able to isolate[5] three more crystalline

[1] For a review of the chemical and pharmacological studies with different parts of the tree up to the year 1949 see R. N. Chopra, I. C. Chopra, K. L. Handa and L. D. Kapur, *Indigenous Drugs of India* pp. 360–363 U. N. Dhur & Sons Private Ltd., Calcutta, India (1958).

[2a] S. Siddiqui, *Curr. Sci.* **11**, 278 (1942); [b] C. Mitra and S. Siddiqui, *Ibid.* **17**, 51 (1948); [c] *J. Sci. & Ind. Res. India* **4**, 5 (1945); [d] C. Mitra, P. N. Rao, S. Bhattacharji and S. Siddiqui, *Ibid.* **6B**, 19 (1947); [e] S. Siddiqui, C. Mitra and S. Bhattacharji, *Ibid.* **8B**, 188 (1949); [f] *Ibid.* **12B**, 154 (1953); [g] C. Mitra, P. N. Rao and S. Siddiqui, *Ibid.* **12B**, 152 (1953).

[3] K. S. Pankajamani and T. R. Seshadri, *Proc. Indian Acad. Sci.* **36A**, 157 (1952).

[4] S. Mukherjee and H. C. Srivastava, *J. Amer. Chem. Soc.* **77**, 422 (1955).

[5] The isolation of these compounds were reported in a short communication, P. Sengupta, S. N. Choudhuri and H. N. Khastgir, *Chem. & Ind.* 861 (1958).

substances besides nimbosterol. The isolation procedure employed consisted in extracting the bark with benzene and separating the benzene extract into (a) a neutral fraction and (b) a sodium hydroxide soluble fraction.

The neutral fraction (a) was partitioned between petroleum ether and aqueous methanol.[6] The oily residue from the petroleum ether extract was saponified with methanolic potassium hydroxide and the unsaponifiable material on chromatography over alumina afforded two crystalline solids. The first solid that was eluted from the column with a mixture of petroleum ether and benzene (7 : 3) melted at 82–83°, $[\alpha]_D$ +7·8°. The compound did not show any maxima or any end absorption in the ultra-violet absorption spectra, thus establishing that it was completely saturated. The molecular formula, $C_{26}H_{54}O$, the hydroxyl peak at 2·9 μ in the infra-red spectra and the optical activity indicated that this compound is a branched chain paraffin alcohol having an asymmetric centre.

The second solid from the chromatogram which was eluted with benzene melted at 136–137°, $[\alpha]_D$ −37·6°. On acetylation it formed an acetate, m.p. 129–130°. The melting points of the alcohol and the acetate were not depressed when mixed with authentic specimens of β-sitosterol and its acetate respectively. Siddiqui *et al.*[2e,f] isolated nimbosterol from the same unsaponifiable fraction and assigned[2d] the molecular formula, $C_{29}H_{24}O$ to it. Nevertheless the melting point of nimbosterol (137°) and its acetate (128°) suggested that nimbosterol was the β-sitosterol isolated by us.[5] Almost simultaneously, Brochere-Ferreol *et al.*[7] arrived at the same conclusion.

The sodium hydroxide soluble fraction (b) reported above was freed from any acidic material by washing with sodium carbonate solution and the phenolic fraction of the bark thus obtained was chromatographed over acid washed alumina. The first crystalline solid eluted from the column was found to be identical with sugiol or 7-ketoferruginol (I, R = H).[8,9] It may be pointed out however that it is for the first time that sugiol has been isolated from a member of the Meliaceae family. So far the occurrence of sugiol has been reported only in several Coniferous species.

The second solid that immediately followed sugiol in the above chromatogram has been assigned the name Nimbiol by us. It melted at 250–251°, $[\alpha]_D$ +32·3° and the elementary analysis corresponded[10] to the molecular formula $C_{18}H_{24}O_2$. The infra-red spectra of nimbiol exhibited peaks at 3·05 μ and 6·03 μ indicating the presence of a phenolic hydroxyl group and a conjugated ketonic carbonyl group respectively. The phenolic nature of nimbiol was exhibited by its solubility in 10 per cent cold sodium hydroxide solution although it failed to give colour with alcoholic ferric chloride solution. Further nimbiol formed a monomethyl ether, $C_{19}H_{26}O_2$, m.p. 142–143° and a monoacetate, $C_{20}H_{26}O_3$, m.p. 111–112°. The infra-red spectra of nimbiol acetate showed the absence of the hydroxyl peak of nimbiol but showed peaks at 5·69 μ and 8·4 μ (phenolic acetate) and 5·97 μ (conjugated ketone). The presence of a carbonyl function in nimbiol was further demonstrated by the formation of a semicarbazone, m.p. 208–210° of nimbiol methyl ether. The presence of an aromatic

[6] Nimbin was isolated from the methanolic layer of the partition, the details of which will be published in a separate communication. See also P. Sengupta, S. K. Sengupta and H. N. Khastgir, *Chem. & Ind.* 1402 (1958); 397 and 1194 (1959).

[7] G. Brochere-Ferreol, J. Polonsky and C. Mitra, *C.R. Acad. Sci., Paris* **246**, 3082 (1958).

[8] J. Simonsen, *The Terpenes* Vol. III, p. 359. University Press, Cambridge (1952).

[9a] C. W. Brandt and B. R. Thomas, *J. Chem. Soc.* 2442 (1952); [b] *New Zealand J. Sci. Technol.* **33B**, No. 1, 30 (1951).

[10] S. N. Choudhuri, H. N. Khastgir and P. Sengupta, *Chem. & Ind.* 634 (1959).

nucleus in nimbiol was indicated by the peaks at 6·25, 6·35 and 6·7 μ in the infra-red spectra of nimbiol.

The presence of *p*-hydroxyphenylketone moiety in nimbiol, as is present in sugiol was indicated by the ultra-violet absorption spectra of nimbiol, which in neutral alcoholic solution exhibited maxima at 231 mμ and 286 mμ. The spectra in 0·1 N NaOH in alcohol exhibited maxima at 251 mμ and 344 mμ. We have observed that

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sugiol in 0·1 N NaOH in alcohol exhibited maxima at 251 mμ and 346 mμ in the ultra-violet region. The ultra-violet absorption spectra of nimbiol acetate showed maxima at 257 mμ and 294 mμ in neutral alcoholic solution. Further that the carbonyl group of nimbiol is present in conjugation with the aromatic nucleus was demonstrated by the fact that on hydrogenation in presence of palladium charcoal catalyst and perchloric acid[11] nimbiol acetate smoothly took up two mole equivalents of hydrogen and afforded deoxonimbiol acetate, $C_{20}H_{28}O_2$, m.p. 102–103°. The latter showed absorption maxima in the ultra-violet at 268 mμ and 277 mμ showing the presence of a substituted phenyl acetate type of chromophore. The infra-red spectra showed the acetate peak at 5·71 and 8·3 μ and the absence of the conjugated carbonyl peak. When nimbiol or its acetate was shaken in an atmosphere of hydrogen in presence of palladium charcoal catalyst without the addition of perchloric acid, there was no appreciable uptake of hydrogen. Evidently nimbiol is devoid of any isolated ethylenic linkage. On the basis of the foregoing experiment coupled with the observations made so far, it may be deduced that nimbiol is tricyclic.

Hydrolysis of deoxonimbiol acetate with methanolic potassium hydroxide furnished deoxonimbiol as a resinous mass, which resisted all attempts at crystallization. The ultra-violet absorption spectra of deoxonimbiol exhibited maxima at 283 mμ

[11] K. W. Rosenmund, E. Karg and F. K. Marcus, *Ber. Dtsch. Chem. Ges.* **75B**, 1850 (1942).

indicating that a phenol has been generated. Deoxonimbiol on reacetylation yielded deoxonimbiol acetate, m.p. 102–103°. Nimbiol on Clemmensen reduction also gave deoxonimbiol, identified as its acetate. It is interesting to point out here that deoxonimbiol was very slightly soluble in aqueous alkali like the diterpene phenols, ferruginol and totarol and in contrast to its parent compound, nimbiol which was fairly readily soluble in dilute alkali.

Finally the interesting compounds obtained by the selenium dehydrogenation of deoxonimbiol under varying conditions gave a clear insight into the structure of nimbiol. On mild dehydrogenation deoxonimbiol gave a phenolic compound, $C_{17}H_{20}O$, m.p. 147–148° (monomethyl ether, m.p. 145–146°) whose ultra-violet absorption spectra strongly indicated that it was a tetrahydrophenanthrol derivative. On more drastic dehydrogenation, in addition to the above tetrahydrophenanthrol, a tetrahydrophenanthrene, $C_{17}H_{20}$, m.p.82– 83° and a new phenanthrol, $C_{16}H_{14}O$, m.p. 189–190° (monomethyl ether, m.p. 119–120°) were isolated. The ultra-violet absorption spectra of this phenanthrol was identical with those of 1-methyl-6-hydroxyphenanthrene, prepared from podocarpic acid.[12] Thus it seemed to us that this phenanthrol, m.p. 189–190° was a dimethylphenanthrol. Our assumption was found to be quite correct, since on still more drastic dehydrogenation, deoxonimbiol gave pimanthrene (1,7-dimethylphenanthrene), m.p. 83–84° along with the phenanthrol, m.p. 189–190°. The melting point of the former was not depressed when mixed with an authentic specimen of pimanthrene. Further the picrate, m.p. 130–131° did not depress the melting point of an authentic specimen.

The foregoing results of selenium dehydrogenation experiments led us to envisage for nimbiol a hydrophenanthrene structure related to tricyclic diterpenes. The isolation of pimanthrene suggested that the phenanthrol, m.p. 189–190° was 1,7-dimethyl-6-hydroxyphenanthrene (V, R = H), the formation of which is conceivable if nimbiol possessed any of the three structures VI, VII or VIII. But the structure VII cannot explain the formation of the C_{17}-tetrahydrophenanthrol, which evidently has the structure IV (R = OH) or of the C_{17}-tetrahydrophenanthrene, which has the structure IV (R = H). Finally, of the alternative structures, VI and VIII, we prefer structure VI for nimbiol, because of its occurrence with sugiol (I, R = H) in the same plant. The rotatory dispersion curves of nimbiol methyl ether and sugiol methyl ether (I, R = Me) are so strikingly similar that we consider this also as a strong evidence in support of structure VI for nimbiol. Further the rotatory dispersion data established the identity of the steric configuration of nimbiol with that of sugiol. The absolute configuration of nimbiol could now be expressed by the structure II (R = H)[13,14] and of deoxonimbiol by the structure III (R = H). This conclusion was further corroborated by chemical evidences.

Recently Wenkert *et al.*[15] discovered that chromic acid oxidation could be employed as a diagnostic tool in elucidating the nature of the A/B ring juncture of a monobenzenoid tricarbocyclic diterpene system. They observed that all *trans* A/B

[12] See Ref. 8, p. 473.
[13] S. N. Choudhuri, H. N. Khastgir and P. Sengupta, *Chem. & Ind.* 1284 (1959).
[14] After the announcement of our structure of nimbiol in a preliminary communication (Ref. 13) Dr. Roy H Bible, Jr. of G. D. Searle & Co., Chicago, Illinois, U.S.A. has kindly informed us that he has synthesized the phenol II (R = H) from podocarpic acid. The synthetic phenol and its methyl ether were found to be identical with our nimbiol and its methyl ether respectively. We are highly indebted to Dr. Bible for this information.
[15] E. Wenkert and B. G. Jackson, *J. Amer. Chem. Soc.* **80**, 211 (1958).

4,4-disubstituted hydrophenanthrenes of the type IX on oxidation with chromic acid invariably yielded 7-keto derivatives, whereas those possessing A/B *cis* ring juncture gave the 6,7-diketo compounds. By using the above method Ghatak[16] assigned the correct stereochemistry to his synthetic desoxypodocarpic acids. In the present study, we exposed deoxonimbiol acetate (III, R = CO·Me) to the action of chromic acid and from the reaction product could isolate only nimbiol. This fact was in conformity with the structure II (R = H) for nimbiol.

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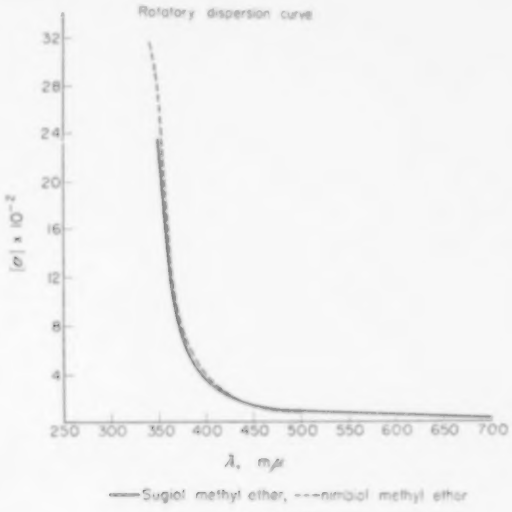

CHART II.

We observed further that neither sugiol methyl ether nor nimbiol methyl ether (II, R = Me) could be condensed with ethyl formate or furfural in presence of base, which could be explained by the fact that the equatorial methyl group at C_4 strongly hindered positon 6, since the A/B ring juncture was *trans* in both these compounds.

The occurrence of sugiol and nimbiol in the same plant is very interesting from the biogenetic point of view.[17] It seems to us that both sugiol and nimbiol could have been formed from a hypothetical pimaric acid type intermediate X. Nimbiol and sugiol might have been formed along Route A and Route B respectively as shown in Chart III on page 50.

EXPERIMENTAL

The petroleum ether used throughout the investigation had b.p. 60–80°.

Examination of the Neutral Fraction of the Trunk Bark of Melia azadirachta *Linn.*

Isolation of the paraffin alcohol, $C_{28}H_{54}O$ *and β-Sitosterol*

1 Kg dried and powdered trunk bark of *M. azadirachta* Linn. was extracted in a Soxhlet with benzene for 30 hr. The resinous mass (25 g) on removal of benzene, was taken up in ether and washed with cold 5% NaOH (4 × 100 cc), then with water and dried (Na_2SO_4). The neutral material (8 g) after removal of ether was dissolved in pet. ether (200 cc) and extracted several times with 80% aqueous methanol (total 200 cc). The dark residue (5·5 g) after evaporation of pet. ether layer was saponified by refluxing for 6 hr with KOH (5 g), methanol (90 cc) and water (10 cc). The ether extract yielded a gummy material (2·5 g). This was chromatographed (alumina, 60 g) and pet. ether

[16] U. R. Ghatak, *Tetrahedron Letters* No. 1, 19 (1959).
[17] For a general scheme for the biogenesis of diterpenes see E. Wenkert and J. W. Chamberlin, *J. Amer. Chem. Soc.* **81**, 688 (1959).

and benzene (7 : 3) eluted a crystalline solid (0·8 g), m.p. 70–74°, while benzene eluted a second crystalline solid (0·45 g), m.p. 125–130°.

The paraffin alcohol, $C_{28}H_{54}O$. The crystalline solids (0·8 g), m.p. 70–74° in the above chromatogram after crystallization from cyclohexane gave the paraffin alcohol (0·09 g), m.p. 82–83°, $[\alpha]_D$ + 7·8° ($CHCl_3$). (Found: C, 81·60; H, 14·13. $C_{28}H_{54}O$ requires: C, 81·59; H, 14·22%). Mol. wt., Found (Rast), 375. Calc., 382,

U.V. No maxima and no end absorption.

I.R. ($CHCl_3$) Peak at 2·9 μ.

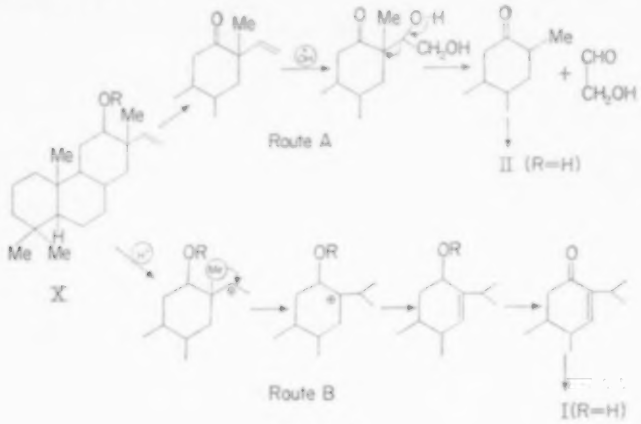

CHART III.

β-Sitosterol. The crystalline solids (0·45 g), m.p. 125–130° eluted with benzene in the above chromatogram were crystallized from methanol, yielding β-sitosterol (0·04 g), m.p. 136–137°, $[\alpha]_D$ −37·6° ($CHCl_3$), identical with an authentic sample of β-sitosterol.

β-Sitosterol acetate. β-Sitosterol (0·16 g) was acetylated with pyridine (2 cc) and acetic anhydride (2 cc) and the *acetate* (0·16 g), m.p. 124–125° crystallized from methanol (0·06 g), m.p. 129–130°, $[\alpha]_D$ −38° ($CHCl_3$), was identical with an authentic sample of β-sitosterol acetate. (Found: C, 82·06; H, 11·24. Calc. for $C_{31}H_{52}O_2$: C, 81·52; H, 11·48%).

Examination of the Phenolic Fraction of the Trunk Bark of Melia azadirachta *Linn.*

Isolation of sugiol (I, R = H) *and nimbiol* (II, R = H)

3·6 Kg dried and powdered trunk bark of *M. azadirachta* was extracted with benzene. The residue was dissolved in ether and extracted with 5% NaOH (4 × 200 cc). This solution after acidification with cold and dil HCl was extracted with ether, washed with cold 5% Na_2CO_3, then with water, and dried (Na_2SO_4). The gummy phenolic residue (12·5 g) was chromatographed over alumina (400 g, deactivated with 12 cc of 10% aqueous acetic acid). Elution with benzene gave crystalline solids (0·52 g), m.p. 260–280°, while elution with a mixture of benzene and ether (9:1) gave a second crystalline solid (0·82 g), m.p. 230–238°.

Sugiol (I, R = H). The crystalline solids (0·52 g), m.p. 260–280° in the above chromatogram were crystallized from methanol, yielding sugiol (0·25 g, 0·007% yield on dried trunk bark), m.p. 292–294° (reported[36] m.p. 295–297°), $[\alpha]_D$ +26° (EtOH). (Found: C, 80·44; H, 9·36. Calc. for $C_{20}H_{28}O_2$: C, 79·95; H, 9·39%). Mol. wt., Found (Rast), 312. Calc., 300.

U.V. (95% EtOH) λ_{max} 232 mμ (log E 4·19) and 284 mμ (log E 4·12) (0·1 N NaOH in EtOH) λ_{max} 251 mμ (log E 3·53) and 346 mμ (log E 4·41)

I.R. (KBr disk) Peaks at 3·2 μ and 6·05 μ.

Sugiol methyl ether (I, R = Me)

(a) To a warm solution of sugiol (0·09 g) in methanol (0·15 cc) and 10% NaOH (0·16 cc) was added dimethyl sulphate (0·04 cc) and the reaction mixture shaken vigorously, cooled and poured

into water. The methyl ether (0·05 g) crystallized from methanol, m.p. 137–138° (Lit.[94] m.p. 138–139°) $[\alpha]_D$ +37·4° ($CHCl_3$). (Found: C, 80·00; H, 9·60. Calc. for $C_{21}H_{30}O_2$: C, 80·21; H, 9·62%).
U.V. (95% EtOH) λ_{max} 231 mμ (log E 4·29) and 280 mμ (log E 4·18).

(b) A mixture of sugiol (0·32 g), dry acetone (25 cc), anhydrous potassium carbonate (2 g) and dimethyl sulphate (1·5 cc) was refluxed for 5 hr, cooled and poured into cold water. Crystallization from methanol gave *methyl ether* (0·25 g), m.p. 137–138°.

Sugiol acetate (I, R = CO·Me). Sugiol (0·11 g) was acetylated with pyridine (2 cc) and acetic anhydride (2 cc) and the *acetate* crystallized from methanol (0·05 g), m.p. 164–165° (Lit[94] m.p. 165–167°).

Sugiol benzoate (I, R = CO·C_6H_5). Sugiol (0·24 g), pyridine (3 cc) and benzoyl chloride (0·24 cc) gave *sugiol benzoate* (0·08 g), m.p. 184° (Lit.[95] m.p. 185–186°).

Nimbiol (II, R = H). The second crystalline solids (0·82 g), m.p. 230–238° eluted with benzene–ether (9 : 1) in the above chromatogram on crystallization from benzene and then from methanol yielded nimbiol (0·42 g, 0·011% yield on dried bark), m.p. 245–247°. Purification gave the analytical sample, m.p. 250–251°, $[\alpha]_D$ +32·3° ($CHCl_3$). (Found: C, 79·14; H, 8·88. $C_{18}H_{24}O_2$ requires: C, 79·37; H, 8·88%). Mol. wt., Found (Rast), 280. Calc., 272.
U.V. (95% EtOH) λ_{max} 231 mμ (log E 4·07) and 286 mμ (log E 4·06) (0·1 N NaOH in EtOH) λ_{max} 251 mμ (log E 3·89) and 344 mμ (log E 4·33)
I.R. ($CHCl_3$) Peaks at 3·05 μ (phenolic hydroxyl), 6·03 μ (conjugated ketone) and 6·25, 6·35 and 6·7 μ (aromatic nucleus).

Nimbiol acetate (II, R = CO·Me). A solution of nimbiol (1·46 g) in pyridine (15 cc) and acetic anhydride (15 cc) was heated on the steam bath for 4 hr. The crude *acetate* m.p. 100–103° was crystallized from aqueous methanol (0·75 g), m.p. 111–112°, $[\alpha]_D$ +22·6° ($CHCl_3$). (Found: C, 76·50; H, 8·70. $C_{20}H_{26}O_3$ requires: C, 76·40; H, 8·34%).
U.V. (95% EtOH) λ_{max} 257 mμ (log E 4·09) and 294 mμ (log E 3·41)
I.R. ($CHCl_3$) Peaks at 5·97 μ (conjugated carbonyl) and 5·69 and 8·4 μ (phenolic acetate).

Hydrolysis of nimbiol acetate: regeneration of nimbiol. Nimbiol acetate (0·1 g) was refluxed with 5% methanolic KOH (2 cc) for 3 hr and extracted with ether. The aqueous alkaline solution on acidification with dil. HCl gave nimbiol, m.p. 244–245°.

Nimbiol methyl ether (II, R = Me)

(a) To a warm solution of nimbiol (0·5 g) in 10% NaOH (1 cc) dimethyl sulphate (0·5 cc) was added with shaking. The ether extract was washed with 10% NaOH, and water and dried (Na_2SO_4). The *methyl ether* crystallized from methanol (0·26 g), m.p. 142–143°, $[\alpha]_D$ +43·7° ($CHCl_3$). (Found: C, 79·14; H, 8·87. $C_{19}H_{26}O_2$ requires: C, 79·68; H, 9·15%).

(b) A mixture of nimbiol (0·38 g), dry acetone (25 cc), anhydrous potassium carbonate (2 g) and dimethyl sulphate (1·6 cc) was refluxed for 5 hr. Crystallization of the product from methanol gave *nimbiol methyl ether* (0·24 g), m.p. 142–143°.

Semicarbazone of nimbiol methyl ether. A mixture of nimbiol methyl ether (0·07 g), semicarbazide hydrochloride (0·07 g), ethanol (5 cc) and pyridine (0·1 cc) was refluxed for 5 hr. The *semicarbazone* (0·04 g), m.p. 208–210° crystallized from methanol. (Found: C, 69·58; H, 8·37. $C_{20}H_{29}O_2N_3$ requires: C, 69·94; H, 8·51%).

Deoxonimbiol acetate (III, R = CO·Me)

(a) A mixture of nimbiol acetate (1·1 g), glacial acetic acid (20 cc), 10% palladium charcoal catalyst (0·5 g) and perchloric acid (0·2 cc) was stirred at room temp in an atmosphere of hydrogen until two molar equivalents were absorbed. The reaction mixture was filtered, diluted with water, and extracted with ether. The ether layer was washed with dil. Na_2CO_3 aq and water, and dried (Na_2SO_4). The oily residue (1·1 g) crystallized from methanol yielding *deoxonimbiol acetate* (0·7 g), m.p. 102–103°, $[\alpha]_D$ +56·4° ($CHCl_3$). (Found: C, 80·35; H, 9·26. $C_{20}H_{28}O_3$ requires: C, 79·95; H, 9·39%).
U.V. (95% EtOH) λ_{max} 268 mμ (log E 2·97) and 277 mμ (log E 2·96).
I.R. ($CHCl_3$) Peaks at 5·71 μ and 8·3 μ (phenyl acetate).

(b) To zinc amalgam, prepared from 1·8 g of zinc, were added conc. HCl (2 cc), water (2 cc) and nimbiol (0·3 g) dissolved in toluene (4 cc) and ethanol (1 cc) and the mixture refluxed for 24 hr. Conc. HCl (0·1 cc) was added to the reaction mixture every hour during the reflux period. The

ether extract was washed with water, dried (Na_2SO_4) and yielded a resinous residue (0·23 g, λ_{max} 283 mμ, log E 3·58) of *deoxonimbiol*. It was acetylated with pyridine (2 cc) and acetic anhydride (2 cc) and the *acetate* (0·2 g) was chromatographed over alumina (10 g, deactivated with 0·3 cc of 10% aqueous acetic acid). On elution with pet. ether, *deoxonimbiol acetate* (0·08 g), m.p. 102–103° was obtained.

Attempted hydrogenation of nimbiol (without perchloric acid). A mixture of nimbiol (0·3 g), ethyl acetate (45 cc) and 10% palladium charcoal catalyst (0·15 g) was stirred in an atmosphere of hydrogen. No absorption of hydrogen took place even after 8 hr, and unchanged nimbiol (0·29 g), m.p. 244–246° was recovered.

Hydrolysis of deoxonimbiol acetate. A solution of deoxonimbiol acetate (1·7 g) in 10% methanolic KOH (10 cc) was refluxed for 4 hr, cooled, acidified with dil. HCl and extracted with ether, yielding a resinous mass (1·1 g) which was insoluble in aqueous alkali and could not be crystallized.
U.V. (95% EtOH) λ_{max} 283 mμ (log E 3·56).

The resinous material on reacetylation in the usual manner gave deoxonimbiol acetate, m.p. 101–103°.

Selenium dehydrogenation experiments

Isolation of 1,1,7-*trimethyl*-6-*hydroxy*-1,2,3,4-*tetrahydrophenanthrene* (IV, R = OH). An intimate mixture of deoxonimbiol (0·8 g) and selenium powder (2 g) was heated at 300–320° for 11 hr. The reaction product was thoroughly extracted with ether and the evaporation product chromatographed over alumina (20 g, deactivated with 2 cc of 10% aqueous acetic acid). The petroleum ether–benzene (1 : 1) eluate (0·33 g), after 3 crystallizations from pet. ether gave 1,1,7-trimethyl-6-hydroxy-1,2,3,4-tetrahydrophenanthrene (0·08 g), m.p. 147–148°. (Found: C, 84·85; H, 8·38. $C_{17}H_{20}O$ requires: C, 84·95; H, 8·39%).
U.V. (95% EtOH) λ_{max} 235 mμ (log E 4·8), 283 mμ (log E 3·7), 316 mμ (log E 3·27) and 330 mμ (log E 3·39).

Methyl ether (IV, R = OMe). A mixture of the above tetrahydrophenanthrol (0·05 g), dry acetone (10 cc), anhydrous potassium carbonate (0·5 g) and dimethyl sulphate (0·4 cc) was refluxed for 5 hr. Crystallization of the product from methanol gave the *monomethyl ether* of the tetrahydrophenanthrol, m.p. 145–146°, not identical with the starting tetrahydrophenanthrol.

Isolation of 1,1,7-*trimethyl*-1,2,3,4-*tetrahydrophenanthrene* (IV, R = H), 1,1,7-*trimethyl*-6-*hydroxy*-1,2,3,4-*tetrahydrophenanthrene* (IV, R = OH) *and* 1,7-*dimethyl*-6-*hydroxyphenanthrene* (V, R = H).

A mixture of deoxonimbiol (1·1 g) and selenium powder (4 g) was heated at 320–340° for 50 hr. The reaction mixture, gave a gummy residue (1 g), which afforded a crystalline solid (0·25 g), m.p. 155–156° from pet. ether. The pet. ether mother liquor was evaporated leaving a gummy residue (0·7 g), which was chromatographed over alumina (40 g), and the gummy residue (0·26 g) eluted with pet. ether was rechromatographed over alumina (26 g). Pet. ether eluted a crystalline solid (0·18 g), m.p. 77–78°, which on crystallization from absolute alcohol gave the tetrahydrophenanthrene (IV, R = H), m.p. 78–79°. On sublimation at 95°/0·2 mm it melted at 82–83°. (Found: C, 90·98; H, 8·99. $C_{17}H_{20}$ requires: C, 91·01; H, 8·99%).
U.V. (95% EtOH) λ_{max} 230 mμ (log E 4·86), 279 mμ (log E 3·73), 310 mμ (log E 3·0) and 324 mμ (log E 3·11).

The pet. ether insoluble solid, m.p. 155–156° reported above was chromatographed over alumina (30 g, deactivated with 1·5 cc of 10% aqueous acetic acid). A mixture of pet. ether and benzene (7 : 3) eluted a solid (0·1 g), m.p. 132–140°, while benzene eluted a second solid (0·1 g), m.p. 179–182°.

The crystalline solids (0·1 g), m.p. 132–140° on recrystallization from pet. ether gave the tetrahydrophenanthrol (IV, R = OH), m.p. 146–148° identical with the tetrahydrophenanthrol reported before.

The crystalline solids (0·1 g), m.p. 179–182° eluted with benzene was rechromatographed over alumina (10 g, deactivated with 0·7 cc of 10% aqueous acetic acid). The benzene eluate gave crystalline solids (0·06 g), m.p. 184–186°, which after crystallization from a mixture of benzene and pet. ether afforded 1,7-dimethyl-6-hydroxyphenanthrene (V, R = H), m.p. 189–190°. On sublimation at 170°/0·2 mm the analytical sample, m.p. 189–190° was obtained. (Found: C, 86·24; H, 6·42. $C_{16}H_{14}O$ requires: C, 86·45; H, 6·35%).

U.V. (95% EtOH) λ_{max} 257 mμ (log E 4·43), 279 mμ (log E 3·97),
298 mμ (log E 3·66), 308 mμ (log E 3·78),
339 mμ (log E 3·13) and 356 mμ (log E 3·15).

Methyl ether (V, R = Me). A mixture of the phenanthrol (0·09 g), m.p. 189–190°, acetone (10 cc), anhydrous potassium carbonate (0·5 g) and dimethyl sulphate (0·4 cc) was refluxed for 10 hr. The product, m.p. 113–115° on crystallization from methanol gave the methyl ether of 1,7-dimethyl-6-hydroxyphenanthrene (0·06 g), m.p. 119–120°. (Found: C, 86·23; H, 6·90. $C_{17}H_{16}O$ requires: C, 86·40; H, 6·83%).

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Isolation of pimanthrene and 1,7-*dimethyl-6-hydroxyphenanthrene* (V, R = H)

A mixture of deoxonimbiol (0·62 g) and selenium powder (3 g) was heated at 340–360° for 42 hr. The product of dehydrogenation (0·6 g) on crystallization from pet. ether and a mixture of benzene and pet. ether gave 1,7-dimethyl-6-hydroxyphenanthrene, identical with the compound reported above.

The residue (0·4 g) obtained on the evaporation of the pet. ether mother liquor above was chromatographed over alumina (30 g). Pet. ether eluted a crystalline solid (0·2 g), m.p. 70–74°, which was rechromatographed over alumina (25 g). After a forerun of an oil (0·06 g), pet. ether eluted a crystalline solid (0·12 g), m.p. 74–78°, which on crystallization from methanol gave *pimanthrene* (0·05 g), m.p. 81°. On sublimation at 100–115°/0·1 mm the analytical sample melted at 83–84° identical with an authentic sample of pimanthrene. (Found: C, 93·04; H, 6·64. Calc. for $C_{16}H_{14}$: C, 93·16; H, 6·84%)
U.V. (95% EtOH) λ_{max} 258 mμ (log E 4·75), 279 mμ (log E 4·11),
288 mμ (log E 4·02), 300 mμ (log E 4·12),
318 mμ (log E 2·47), 327 mμ (log E 2·35),
333 mμ (log E 2·5), 339 mμ (log E 2·29) and
350 mμ (log E 2·24).

Pimanthrene picrate. The picrate, prepared in the usual manner m.p. 130–131° was not depressed when mixed with an authentic specimen of pimanthrene picrate.

1-*Methyl-6-hydroxyphenanthrene.*[12] Podocarpic acid was dehydrogenated with palladium charcoal catalyst and 1-methyl-6-hydroxyphenanthrene, m.p. 160° was isolated in the usual manner.
U.V. (95% EtOH) λ_{max} 257 mμ (log E 4·6), 279 mμ (log E 4·0),
297 mμ (log E 3·94), 306 mμ (log E 4·02),
340 mμ (log E 3·27) and 357 mμ (log E 3·32).

Attempted preparation of the furfurylidine derivative of (*a*) *sugiol methyl ether and* (*b*) *nimbiol methyl ether*

(a) A mixture of sugiol methyl ether (0·18 g), 95% ethanol (10 cc), 15% NaOH (0·36 cc), freshly distilled furfural (0·1 cc) and water (1 cc) was kept at room temp. for 4 hr. On working up unchanged sugiol methyl ether (0·15 g), m.p. 137–138° was recovered.

(b) From a similar reaction mixture of nimbiol methyl ether (0·2 g), 95% ethanol (10 cc), 15% NaOH (0·4 cc), furfural (0·11 cc) and water (1 cc) was recovered unchanged nimbiol methyl ether (0·17 g), m.p. 138–140°.

Attempted condensation of ethyl formate with (*a*) *sugiol methyl ether and* (*b*) *nimbiol methyl ether*

(a) A solution of sugiol methyl ether (0·15 g) in benzene (10 cc) was added with swirling to a cooled mixture of ethyl formate (0·2 g), sodium hydride (0·05 g) and benzene (5 cc). The mixture was allowed to stand overnight. On working up unchanged sugiol methyl ether (0·12 g), m.p. and mixed m.p. 136–137° was recovered.

(b) A similar reaction of nimbiol methyl ether (0·15 g) in benzene (20 cc) with ethyl formate (0·2 g), sodium hydride (0·05 g) and benzene (5 cc) gave unchanged nimbiol methyl ether (0·11 g), m.p. and mixed m.p. 138–140°.

Chromic acid oxidation of deoxonimbiol acetate. Deoxonimbiol acetate (0·1 g) was oxidized in glacial acetic acid (1 cc) and chromic acid (0·13 g) in 80% acetic acid (0·6 cc). The gummy product (0·08 g) isolated by means of chloroform was hydrolysed by refluxing for 5 hr with 5% methanolic KOH (2 cc), and extracted with ether. The aqueous alkaline solution was acidified and extracted with ether yielding a residue (0·05 g), m.p. 240–244°, which on crystallization from benzene afforded *nimbiol*, m.p. and mixed m.p. 246–248°.

Acknowledgements—We are indebted to Prof. Carl Djerassi of Stanford University, Stanford, California, U.S.A. for the optical rotatory dispersion data, to Dr. D. Todd of the Worcester Polytechnic Institute, Worcester, Mass., U.S.A. for the gift of the podocarpic acid, to Prof. B. K. Bhattacharyya of Jadavpore University, Calcutta for the authentic samples of β-sitosterol and its acetate and to Dr. D. Nasipuri of the University College of Science, Calcutta for the authentic samples of pimanthrene and its picrate. Our thanks are due to Dr. R. R. Engle of Wayne State University, Detroit, Michigan, to Mrs. Dolores J. Phillips of Baird Atomic Inc., Cambridge, Mass. and to Dr. Tapan K. Mukherji of M. I. T., Cambridge, Mass., U.S.A. for the infrared spectra of our compounds. We are also indebted to Mr. Priyalal Moulik for the optical rotation study and to Mr. N. Guha for encouragement.

Tetrahedron, 1960, Vol. 10, pp. 55 to 64. Pergamon Press Ltd. Printed in Northern Ireland

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REACTIONS CATALYSED BY ALUMINIUM CHLORIDE—XXVIII*

THE REACTION OF CYCLOALKANES WITH CARBON MONOXIDE

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(*Received* 1 *January* 1960)

Abstract—The condensation of some cycloalkanes with carbon monoxide under pressure, in the presence of $AlCl_3$ at normal or slightly higher temperature has been investigated. Cyclopentane leads to cyclopentanecarboxylic acid. Methylcyclopentane yields the same products as cyclohexane, namely cyclohexanecarboxylic acid and 2-methylcyclohexanone. From methylcyclohexane, cyclohexyl methyl ketone is obtained together with a mixture of *trans*-2-methyl-cyclohexanecarboxylic acid with the 3- and/or 4-methyl isomers. From decalin, *trans–trans*-1-decalin-carboxylic acid and *trans*-hexahydro-α-benzosuberone are produced. The mechanism of these reactions is discussed.

IT was established during 1931–1936[1–3] that saturated hydrocarbons C_xH_y react with carbon monoxide under pressure in the presence of aluminium chloride at normal or slightly elevated temperature, yielding three kinds of products: (i) acid $C_xH_{y-1}COOH$; (ii) lower ketone $C_{x+1}H_yO$; (iii) higher ketone $(C_xH_{y-1})_2CO$.

The reaction has been applied to the following hydrocarbons: (Table 1).

Alkanes. Propane,[4–6] n-butane,[3] isobutane,[3] n-pentane,[1,7] isopentane,[1,7] n-hexane[1] and isohexanes.[8]

Cycloalkanes. Cyclohexane.[1,2,7,9]

In order to explain this reaction, a mechanism was suggested[3,4,9] involving the intermediate formation of the formyl cation as in the Gattermann–Koch reaction. This explanation was adopted in most reviews and monographs describing the reaction between alkanes and carbon monoxide.[10]

But, as shown recently,[6] a different mechanism involving the reaction between carbon monoxide and a carbonium ion generated by the hydrocarbon under the influence of the catalyst, is much more probable.

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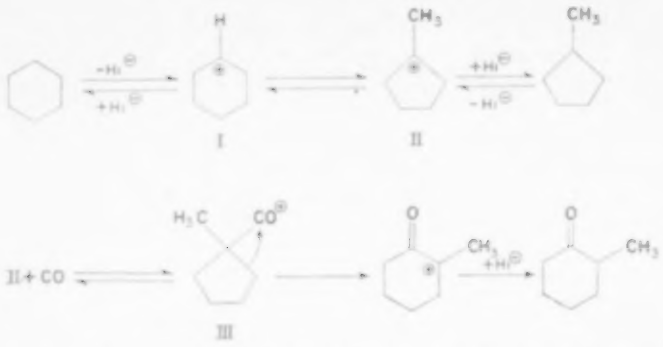
M. Orchin and I. Wender, *Catalysis* (Edited by P. H. Emmett) Vol. 5, p. 1. Reinhold, New York (1957).

This new mechanism when applied to cyclohexane leads to the following scheme:



In fact, the lower ketone obtained in this reaction from cyclohexane[1,2] is indeed 2-methylcyclohexanone, but the acid simultaneously formed is not 1-methyl-cyclopentanecarboxylic acid corresponding to the ions II and III, but instead cyclo-hexanecarboxylic acid, corresponding to the ion I.

In order to gather more experimental data, the reaction was applied to the following cycloalkanes:

1. The condensation of carbon monoxide with *cyclohexane* confirmed the results[1] that the acid produced is mostly cyclohexanecarboxylic acid.

2. The reaction of *methylcyclopentane* yields the same products in nearly the same amounts as in the previous case.

3. The reaction of *cyclopentane* requires heating at 70° and affords cyclopentane-carboxylic acid and dicyclopentylketone (as the higher ketone). The lower ketone is present only in traces.

4. *Methylcyclohexane* readily reacts at room temperature, yielding in appreciable amount cyclohexyl methyl ketone. The acid formed is a mixture of isomeric acids $C_8H_{14}O_2$, which by partial esterification and hydrolysis may be separated into two nearly equal fractions. The fraction difficulty esterified and hydrolysed is *trans*-2-methyl-cyclohexanecarboxylic acid; the other fraction, with higher melting amide, probaby is a mixture of 3- and 4-methyl-cyclohexanecarboxylic acids.

5. Particularly interesting is the reaction of *decalin* with carbon monoxide which proceeds smoothly at room temperature, giving *trans–trans*-1-decalin-carboxylic acid and *trans*-hexahydro-α-benzosuberone.

DISCUSSION OF THE RESULTS

Alkanes and cycloalkanes possessing tertiary carbon atoms react at room temperature and yield all three types of products i–iii. The hydrocarbons which have only primary and secondary carbon atoms and which cannot acquire tertiary carbon atoms by isomerization, such as propane and cyclopentane, react at temperatures above 60° and do not yield lower ketones (ii) because these are probably destroyed under existing conditions.

The reactions have an induction period, easily observed in the case of methyl-cyclohexane or decalin which react at room temperature. The effect of water addition to the reaction mixture (as the crystalohydrate $AlCl_3 \cdot 6H_2O$) results in a reduction of

the induction period, an increase in acid yield and the formation of unsaturated products and gums.

The non-acid higher fractions are a complex mixture of higher ketones (iii), condensation products of the ketones (ii) and (iii), condensation products of aldehydes eventually formed by hydride-ion reduction of acyl cations, and dimeric hydrocarbons resulting from dehydrogenation. This renders difficult the isolation of pure substances, therefore the higher ketones (iii) have been isolated only when the lower ketone is formed in minute amounts (propane[6] and cyclopentane).

Table 1 groups the structures and approximate yields (mole %) of the reaction products obtained from paraffinic hydrocarbons and carbon monoxide under pressure in the presence of aluminium chloride.

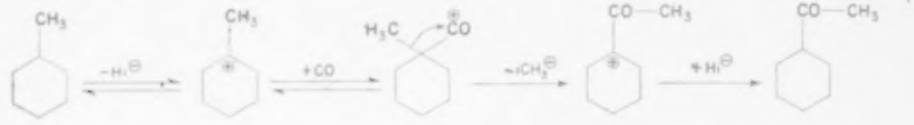
MECHANISM OF THE REACTION

The identity of products obtained from cyclohexane and methylcyclopentane (No. 8), proves that in this case isomerization is more rapid than condensation with carbon monoxide. On the other hand, reactions No. 2 and 3 yield different acids and higher ketones, indicating that the isomerization

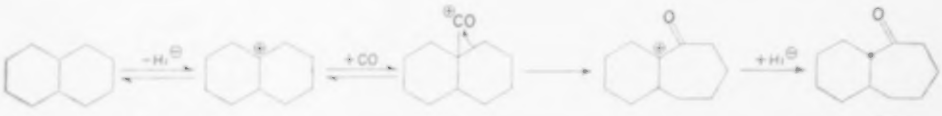
$$CH_3\cdot\overset{\oplus}{C}H\cdot CH_2\cdot CH_3 \underset{?}{\rightleftharpoons} (CH_3)_3C^{\oplus}$$

is slower then the reaction with carbon monoxide.

The mechanism previously proposed[6] is in good agreement with the formation of the lower ketone obtained in all these cases:



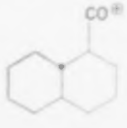
IV



V VI

The rearrangement of tertiary acyl cations to lower ketones always yields the least tensioned possible ring. From III a six-membered ring is formed by expansion; IV already has a six-membered ring and conserves it by methyl migration; while V can by no means yield a 5- or 6-membered ring and therefore expands its cycle to a 7-membered ring.*

* It is supposed that hexahydro-α-benzosuberone is formed through V and not through VII (although the latter is common both to the acid and the lower ketone formed from decalin) since VII ought to yield in



VII

comparable amounts hexahydro-α-benzosuberone as well as -β-, and since no β-derivative is formed.

TABLE 1. STRUCTURE AND YIELDS OF PRODUCTS OBTAINED IN THE REACTION BETWEEN SATURATED HYDROCARBONS, CO AND $AlCl_3$

No.	Hydrocarbon	(i) Acid	(ii) Lower ketone	(iii) Higher ketone
1	$CH_3{\cdot}CH_2{\cdot}CH_3$	$(H_3C)_2CH{\cdot}COOH$ 4[1]; 2[5]	$CH_3{\cdot}CH_2{\cdot}CO{\cdot}CH_3$?[2]; 0[6]	$(H_3C)_2CH{\cdot}CO{\cdot}CH_2{\cdot}CH(CH_3)_2$?[2]; 18[6]
2	$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH_3$	$CH_3{\cdot}CH_2{\cdot}CH(CH_3){\cdot}COOH$?[2] and $(H_3C)_3C{\cdot}COOH$ Traces[3]	$(H_3C)_2CH{\cdot}CO{\cdot}CH_3$ 6[3]	$(H_3C)_2CH{\cdot}CH_2{\cdot}CO{\cdot}CH(CH_3){\cdot}CH_2{\cdot}CH_3$?[2]
3	$(H_3C)_3CH$	$(H_3C)_3C{\cdot}COOH$ 1[3]	$(H_3C)_2CH{\cdot}CO{\cdot}CH_3$ 31[3]	$(H_3C)_2CH{\cdot}CH_2{\cdot}CO{\cdot}C(CH_3)_3$ 4[3]
4	$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_3$	$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH(CH_3){\cdot}COOH$ 5[1]	$(H_3C)_2CH{\cdot}CO{\cdot}CH_2{\cdot}CH_3$ 17[1]	
5	$(H_3C)_2CH{\cdot}CH_2{\cdot}CH_3$		$(H_3C)_2CH{\cdot}CO{\cdot}CH_2{\cdot}CH_3$ 7[1]	
6	$(H_3C)_2CH{\cdot}CH_2{\cdot}CH_2{\cdot}CH_3$ and $CH_3{\cdot}CH_2{\cdot}CH(CH_3){\cdot}CH_2{\cdot}CH_3$		$(H_3C)_2CH{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CH_3$?[2]	

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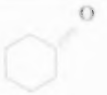
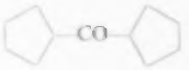
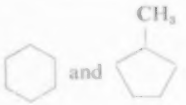
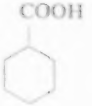
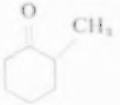
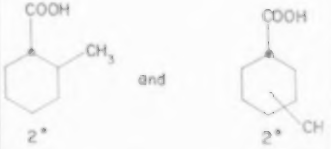
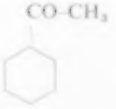
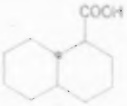
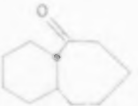
TABLE 1 (*continued*)

No.	Hydrocarbon	(i) Acid	(ii) Lower ketone	(iii) Higher ketone
7		5*	 Traces*	 8*
8		 1[1]; 2*	 4[1],*	
9		 2* and 2*	 26*	
10		 3*	 4*	

* Present work

The mechanism, however, does not account for the structure of the acids obtained in cases No. 2, 4, 8, 9, 10, since these are predominantly secondary (arising therefore from secondary carbonium ions)* though all lower ketones are derived from tertiary carbonium ions. The only instances when both the acid and the lower ketone originate in the same carbonium ion are isobutane (No. 3) which can form a tertiary but no secondary carbonium ion, and propane and cyclopentane (Nos. 1 and 7) which can form only secondary carbonium ions.

The formation of secondary carboxylic acids is surprising for two reasons: Firstly, tertiary alkyl carbonium ions are more stable than secondary ions and ought therefore to be favoured. Secondly, as Koch[11] recently discovered, on treating alkenes or alcohols with anhydrous formic acid in the presence of concentrated sulphuric acid, tertiary carboxylic acids and no secondary acids or ketones are obtained. For this reaction a mechanism was proposed[11] essentially identical with the mechanism suggested[6] for the reaction of alkanes with CO in the presence of $AlCl_3$.[12] It is evident that the mechanism of these two reactions must be different in order to account for the formation of different reaction products.

It was suggested[13] that mixed anhydrides of tertiary carboxylic acids with sulphuric acid and not free tertiary acyl cations are involved in Koch's reaction. This idea seems logical, since the anion $HO—SO_2—O^{\ominus}$ is a stronger nucleophile than $AlCl_4^{\ominus}$. The greater stability of tertiary acids under these conditions may be thus explained, but unfortunately the existence of such mixed anhydrides has not yet been experimentally proved.

The mechanism of the reaction between alkanes or cycloalkanes and carbon monoxide can be interpreted starting from a theory developed by Baddeley[14] for the explanation of certain anomalous isomerizations of alkyl groups in the Friedel–Crafts reaction applied to higher alkyl halides.† According to this author, equilibria between all forms of alkyl carbonium ions (energetically possible) are established in the presence of $AlCl_3$, by $Alk^{\ominus}$ or $H^{\ominus}$ shifts. In these equilibrium mixtures, tertiary carbonium ions will be present in far larger concentrations than secondary carbonium ions, because the former are more stable, but secondary carbonium ions are postulated to react more rapidly than tertiary ones.

In addition, a new feature must be taken into account, namely, that tertiary acyl

* The proportion of tertiary acids contained in the secondary acids may be qualitatively inferred: with No. 2 the tertiary acid is formed in amounts large enough to allow isolation; with No. 8 isolation is not possible but the tertiary acid depresses substantially the melting point of the crude amide; and with No. 10, the amount of tertiary acid is negligible, the crude amide being almost pure.

† An alternative theory which is better supported by experimental data explains these anomalous Friedel–Crafts reactions on the basis of a newly discovered rearrangement of phenyl-alkanes, independent of, and subsequent to, the Friedel–Crafts reaction.[15] As yet no evidence of a similar isomerization of carboxylic acids in the presence of aluminium chloride being available, Baddeley's theory is the best alternative for the explanation of the structure of acids formed in the reaction between alkanes or cycloalkanes and carbon monoxide.

[11] H. Koch, *Brennstoffchemie* **36**, 321 (1955); *Fette, Seif. Anstrichmittel* **59**, 493 (1957); *Riv. Combust.* **10**, 77 (1956);
H. Koch and W. Haaf, *Angew. Chem.* **70**, 311 (1958); *Liebigs Ann.* **618**, 254 (1958).

[12] J. R. Roland, J. D. C. Wilson and W. E. Hanford, *J. Amer. Chem. Soc.* **72**, 2122 (1950).
W. Hanford and D. E. Sargent, *Organic Chemistry. An Advanced Treatise* (Edited by H. Gilman) Vol. IV, pp. 1001–1019. John Wiley, New York (1955).

[13] I. T. Eidus and K. V. Pusytsky, *Proceedings of Communications presented at the 8th Mendeleev Congress of General and Applied Chemistry, Organic Chemistry and Technology Section* p. 113. Ed. Acad. Sci. U.S.S.R., Moscow (1958).

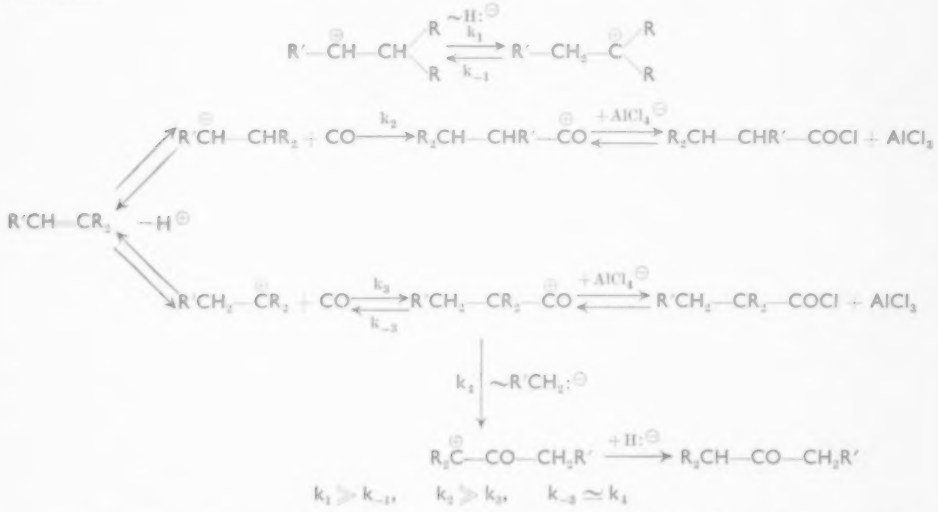
[14] G. Baddeley, *Quart. Rev.* **8**, 355, 366 (1954).

[15] C. D. Nenitzescu, I. Necsoiu, A. Glatz and M. Zalman, *Chem. Ber.* **92**, 10 (1959).

cations are formed reversibly from carbon monoxide and tertiary alkyl carbonium ions. At normal pressure decarbonylation is favoured; furthermore, these tertiary acyl cations may undergo rearrangement.[6]

The complex picture emerging from these considerations may be summarized as follows. Water-activated aluminium chloride abstracts hydride ions from methylene and methine groups yielding secondary and tertiary alkyl carbonium ions; these are subsequently undergoing hydride or alkyl shifts, hydrogen ion eliminations and reaction with carbon monoxide. The latter reaction yields acyl cations; when secondary, these are stable and irreversibly formed, but when tertiary, they decompose reversibly, or rearrange to lower ketones. Thus, the acids present in the final reaction mixture will be predominantly secondary, while the lower ketone will be exclusively derived from tertiary acyl cations. The higher ketones are formed by acylation (with secondary and tertiary acyl cations) of the olefins resulting by hydrogen-ion elimination, and will generally be complex mixtures. The relative concentrations and rates of isomerization and carbonylation of tertiary and secondary alkyl carbonium ions are too complex to be fully understood at present.

The following qualitative scheme accounts for the structure of the acid and lower ketone:



It must be mentioned that when a stationary concentration of carbonium ions is achieved, intermolecular hydride shifts may occur by an ionic chain mechanism, as indicated by the existence of an induction period.

EXPERIMENTAL

All analyses were performed by Miss E. Sliam and Miss V. Săndulescu.

1. *Cyclopentane*

A mixture of 540 g (7·7 moles) cyclopentane (b.p. 49–50°) and 758 g (5·7 moles) aluminium chloride were introduced into a steel autoclave with carbon monoxide compressed to 130 atm. At room temp no absorption takes place even after 72 hr. On heating to 70–80°, 120 l NTP (5·3 moles) CO are absorbed during 8 hr. The contents of the autoclave were hydrolysed with ice and HCl, and extracted with ether. The organic layer was treated with 10% NaOH solution,

yielding after acidification 114 g acid, from which 40 g b.p. 210–215°, were identified as *cyclopentanecarboxylic acid* (4·6% yield). For better purification it was esterified with ethanol in the presence of benzenesulphonic acid, fractionated and hydrolysed with 30% NaOH. (Found, neutral equivalent, 116; $C_6H_{10}O_2$ requires: 114). The *amide* of the crude acid has m.p. 168–169° (from water) and after esterification and hydrolysis m.p. 172°. Lit. 178°,[16] 177–178°.[17] (Found: C, 63·68; H, 9·80; N, 12·38. Calc. for $C_6H_{11}NO$ (113·2): C, 63·91; H, 9·81; N, 12·29%). The mixed m.p. with an authentic sample[16] showed no depression. The *anilide*, m.p. 160°, crystallizes from dil. methanol. (Found: N, 7·40. $C_{12}H_{15}NO$ (189·25) requires: N, 7·49%). The p-*toluidide*, m.p. 134°, crystallizes from methanol. (Lit.[17] 135°).

The non-acid reaction product fractionated at normal, and also at reduced pressure, yields traces of lower ketone, $b.p._{16}$ 45–55° (2,4-dinitrophenylhydrazone m.p. 143–145°, raised by recrystallizations from ethanol; mixed m.p. with authentic *cyclohexanone* 2,4-dinitrophenylhydrazone 162°), and a fraction $b.p._2$ 85–90°, which contains *dicyclopentyl-ketone*, purified by regeneration from its semicarbazone, after which treatment it did not decolourize bromine water. B.p. 251°, n_D^{20} 1·479 d_4^{20} 0·9663. The *semicarbazone*, m.p. 167–168°, crystallizes from methanol. (Lit. 158–162°,[18] 165°,[19] 167°[20]). The 2,4-*dinitrophenylhydrazone*, m.p. 103°, crystallizes from methanol. (Lit. 103–104°[20]).

2. *Cyclohexane*

A mixture of 1000 g (12 moles) cyclohexane and 1850 g (14 moles) aluminium chloride absorb in 12 hr at 20° 10 moles CO (the absorption beginning after short heating at 60°). The mixture, similarly worked up, yields 52 g 2-*methylcyclohexanone* b.p. 160–167°. The *semicarbazone* has a m.p. 192°. (Lit. 197°[21–23] on rapid heating). The 2,4-*dinitrophenylhydrazone*, m.p. 132°, (Lit.[23] 135·5–137° cor.) gave no depression with an authentic specimen.

The acid product (90 g), isolated as above, distilled at 20 mm yielded after a 15 g forerun, a 32 g fraction $b.p._{20}$ 130–140°, containing mostly *cyclohexanecarboxylic acid*. This crude acid gives an *amide* m.p. about 130°. Since fractionation does not allow further purification, use was again made of incomplete esterification and hydrolysis (the tertiary acids or the sterically hindered secondary acids may be thus eliminated from secondary acids, since the former are esterified and hydrolysed much more slowly than the latter). The *amide* prepared from the purified acid m.p. 169° (from water), showed no depression with an authentic sample of m.p. 183°. (Lit.[22] m.p. 184°). The *anilide*, m.p. 138°, was prepared from the chloride of the purified acid and crystallized from aqueous ethanol. A mixed m.p. with authentic cyclohexanecarboxanilide m.p. 143°. (Lit.[23] m.p. 143–144°) showed no depression. (Found: N, 6·89. Calc. for $C_{13}H_{17}NO$ (203·3): N, 6·89%).

3. *Methylcyclopentane*

A mixture of 113 g (1·4 moles) dry, olefin-free methylcyclopentane in a sealed glass tube (prepared by catalytic hydrogenation of 1-methylcyclopentene with 5% Pt on charcoal, and carefully refined and fractionated, b.p. 72–73°) and 180 g (1·35 moles) $AlCl_3$ was introduced into an autoclave. Then carbon monoxide at 50 atm and room temp, was introduced causing the glass tube to break and the hydrocarbon to react with $AlCl_3$. After 6 hr rocking at room temp, the autoclave was opened and the mixture worked up as before. About half of the initial hydrocarbon was recovered. The reaction product contained 1·2 g unitary acid (giving *amide* m.p. 179–181° and *anilide* m.p. 141–142° which did not depress a mixed m.p. of *cyclohexanecarboxylic acid* derivatives), and 32 g neutral product, of which 6 g had a b.p. 150–170°. This fraction readily yields a *semicarbazone* m.p. dec. 191–192° and a 2,4-*dinitrophenylhydrazone* m.p. 133°, identical with the corresponding derivatives of 2-*methylcyclohexanone*.

4. *Methylcyclohexane*

A mixture of 770 g (7·8 moles) methylcyclohexane and 810 g (6·1 moles) $AlCl_3$ were treated in an autoclave at room temp with CO at 150 atm. The pressure began to drop after an induction

[16] C. D. Nenitzescu and I. P. Cantuniari, *Ber. Dtsch. Chem. Ges.* **65**, 807 (1932).
[17] W. O. Ney, W. W. Crouch, C. E. Rannefeld and H. L. Lochte, *J. Amer. Chem. Soc.* **65**, 770 (1943).
[18] J. von Braun, *Ber. Dtsch. Chem. Ges.* **67**, 218 (1934).
[19] C. D. Nenitzescu and E. Ciorănescu, *Ber. Dtsch. Chem. Ges.* **69**, 1820 (1936).
[20] E. A. Braude and W. F. Forbes, *J. Chem. Soc.* 1755 (1951).
[21] H. H. Strain, *J. Amer. Chem. Soc.* **57**, 760 (1935).
[22] O. Aschan, *Liebigs Ann.* **271**, 264 (1892).
[23] H. W. Underwood and J. C. Gale, *J. Amer. Chem. Soc.* **56**, 2119 (1934).

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period of about 10 hr and ceased after the absorption of 7·2 moles CO. The reaction mixture was worked up as before.

Distillation of the neutral product gave two main fractions. The first fraction, b.p.$_5$ 60–80° 288 g, and a second fraction, b.p.$_5$ 120–138°, 175 g (no definite compound could be isolated from this second fraction; possibly it contained sterically hindered esters of methyl-cyclohexanecarboxylic acids, since on treatment with conc. H_2SO_4, an acid mixture was obtained similar to the acid reaction product). The first fraction on refractionation at normal pressure yielded 220 g of a colourless liquid, b.p. 176°, which did not decolourize bromine water, and proved to be *cyclohexyl methyl ketone*; *semicarbazone* m.p. and mixed m.p. 176° (Lit. 175°[19,24]); 2,4-*dinitrophenylhydrazone* m.p. 141° (Lit. m.p. 140°[25]). The reaction with NaOBr yields *cyclohexanecarboxylic acid*, b.p.$_5$ 100°, characterized through its *amide* (m.p. and mixed m.p. 184°) and *anilide* (m.p. and mixed m.p. 143–144°).

TABLE 2

Recrystallization	Crude	1	2	3
Solvent		20% Ethanol	Benzene	Water
Non-esterified acid	147°	159–161°	162°	167°
Acid from ester	151°	165–170°	170°	176°
Mixed m.p.	138°	142°	142°	145°

The acid reaction product (49 g fraction b.p.$_4$ 100–120°) was redissolved in 10% NaOH, extracted with ether to remove traces of non-acid products, acidified and refractionated yielding a colourless liquid, b.p.$_4$ 102°, b.p.$_{760}$ 238°. (Found: C, 67·57; H, 9·92. Neutral equivalent 143. Calc. for $C_8H_{14}O_2$ (142·2): C, 67·32; H, 9·71%. Neutral equivalent 142·2. This acid was first believed to be unitary since the m.p. of the amide (m.p. 145–146°) could not be raised by recrystallization from dil. ethanol but the m.p. of the amide (m.p. 145–146°) could not be raised by recrystallization from dil. ethanol or benzene. (Found: C, 67·71; H, 10·66; N, 9·82; $C_8H_{15}NO$ (141·2) requires: C, 68·04; H, 10·71; N, 9·92%); the *anilide* m.p. 112°. (Found: N, 6·72; $C_{14}H_{19}NO$ (217·3) requires: N, 6·45%).

The acid proved to be a mixture of isomeric $C_8H_{14}O_2$ acids and 35 g were esterified with ethanol–benzene–$C_6H_5SO_3H$, by refluxing 2 hr. This resulted in 20 g ester b.p.$_{45}$ 121°, b.p.$_{760}$ 202°, and 10 g *non-esterified acid*, b.p.$_{50}$ 160°. The ester was refluxed 8 hr with 10% aqueous NaOH, the unsaponified ester extracted with ether, and the solution acidified, resulting in 12 g *acid from ester*. These two acids were converted (through their chlorides, prepared with $SOCl_2$ at room temp) into amides which were consecutively recrystallized. Table 2 shows the m.p. of, and the mixed m.p. between, these amides.

Both amides depress the m.p. of cycloheptanecarboxamide (m.p. 192°), 2,3-dimethyl-cyclopentanecarboxamide (m.p. 170°) and cyclohexaneacetamide (m.p. 167°). But the amide of the *non-esterified acid* with m.p. 167° does not depress the m.p. of trans-2-*methyl-cyclohexanecarboxamide* with m.p. 182–183°.[26] The amide of the *acid from ester* with m.p. 176° is identical with the amide (with m.p. 176°) prepared by oxidation with NaOBr of the ketone obtained in the Nenitzescu reaction between cycloheptene, acetyl chloride, cyclohexane and $AlCl_3$.[27] Thus, the acid which is difficulty esterified is 2-*methyl-cyclohexanecarboxylic acid*, and the acid from ester probably is a mixture of trans-3- and trans-4-*methyl-cyclohexanecarboxylic acids*.[28]

If, before admitting CO, the autoclave is further charged with 0·2–0·5 moles finely ground $AlCl_3 \cdot 6H_2O$, the absorption begins earlier and the acid is formed in larger amounts and contains a white gum (polymer), little soluble in ether, which separates on acidification of the alkaline solution.

5. *Decalin*

Decalin, 1410 g (10·2 moles) distilled over sodium were introduced in a steel autoclave containing 1140 g (8·5 moles) $AlCl_3$ at −20°, then CO at 150 atm was introduced. The autoclave was rotated

[25] H. G. Walker and C. R. Hauser, *J. Amer. Chem. Soc.* **68**, 1386 (1946).
[26] M. Mousseron, R. Jacquier, M. Mousseron-Canet and R. Zagdoun, *C.R. Acad. Sci., Paris* **235**, 177 (1952); Cf. also W. K. Johnson, *J. Org. Chem.* **24**, 864 (1959).
[27] A. K. Macbeth, J. A. Mills and D. H. Simmonds, *J. Chem. Soc.* 1011 (1949).
[28] C. D. Nenitzescu, I. Pogany and G. Mihai, *Studii Cerc. Chim.* **6**, 375 (1958).
[28] S. L. Friess and R. Pinson, *J. Amer. Chem. Soc.* **73**, 3512 (1951).

and allowed to warm to room temp. The absorption began after about 8 hr, and after 36 hr 242 l NTP CO (10·8 moles) had been absorbed. The mixture was worked up as before, and the neutral product carefully fractionated under reduced pressure. After a forerun of 300 g unreacted decalin, a 55 g fraction b.p.$_2$ 102–114° was collected (leaving 800 g higher-boiling products, which were not further investigated). The fraction yielded on redistillation *hexahydro-α-benzosuberone*, b.p.$_2$ 111°, b.p.$_{760}$ 258°. The *semicarbazone*, m.p. 220°, crystallized from ethanol or from benzene. Lit. 222–223° cor.;[29] 213–214°.[30] (Found: C, 64·63; H, 9·74; N, 18·88. Calc. for $C_{12}H_{21}N_3O$ (220·3): C, 64·54; H, 9·48; N, 18·82%). The 2,4-*dinitrophenylhydrazone*, brick-red, m.p. 168° crystallized from ethanol–benzene. Lit. m.p. 176·5–177 cor.;[29] 173–174°.[30] (Found: N, 16·25. Calc. for $C_{12}H_{12}N_4O_4$ (346·4): N, 16·18%). The mixed m.p. and I.R. spectra of the *semicarbazone* and *dinitrophenylhydrazone* show identity with authentic products.[29]

The acid product gave a 45 g fraction b.p.$_2$ 140–150° (leaving 42 g higher-boiling products), which redissolved in 10% NaOH solution, extracted with ether, acidified and refractionated on a short column yielded a unitary acid b.p.$_3$ 158°, b.p.$_{760}$ 275°, as a colourless very viscous liquid, which slowly crystallized, m.p. 94–98°. This acid proved to be trans–trans-1-*decalincarboxylic acid*. Lit. m.p. 101·5–102·5°;[29] 102°;[31] 96–98°;[32] 87–88°.[33] (Found: C, 72·68; H, 9·78; neutral equivalent 183. Calc. for $C_{11}H_{18}O_2$ (182·2): C, 72·49; H, 9·95%, neutral equivalent 182·2). The *amide* was prepared by means of the acid chloride, at room temp, with the precautions recommended by Dauben and Hoerger,[34] and had m.p. 218–220°. (Lit. 223–224°;[29] 223°;[31] 206–208°;[32] 222–223°.[33]). The p-*bromophenacyl ester*, m.p. 125°, crystallized from ethanol. (Found: C, 60·39; H, 6·27; Br. 20·43. $C_{19}H_{23}BrO_3$ requires: C, 60·16; H, 6·11; Br. 21·07%). The *anilide*, little soluble in ether, has m.p. 187° and crystallized from 80% ethanol. (Found: N, 5·54. $C_{17}H_{23}NO$ (257·4) requires: N, 5·44%). The p-*toluidide*, m.p. 200–201°, slightly soluble in ether, crystallized from ethanol. (Found: N, 5·23. $C_{18}H_{25}NO$ (271·4) requires: N, 5·16%).

The Schmidt degradation of the acid yielded trans–trans-1-*decalyl-amine*, whose N-*acetyl-derivative* melted at 184–185° and crystallized from 80% methanol. Lit. m.p. 184°;[35] 182°.[31,35] (Found: N, 7·21. Calc. for $C_{12}H_{21}NO$ (195·3): N, 7·17 %). The N-*benzoyl-derivative*, m.p. 195–196°, crystallized from 80% methanol. Lit. m.p. 195°;[31,35,35] 194–195°.[32] The N-*benzenesulphonyl-derivative*, m.p) 141–142°, crystallized from 60% methanol. (Found: C, 65·19; H, 7·65. $C_{18}H_{23}NO_2S$ (293·4. requires: C, 65·49; H, 7·90%). The *picrate*, m.p. 210°, crystallized from water. (Found: C, 50·44; H, 6·08. $C_{18}H_{19}N{\cdot}C_6H_3N_3O_7$ (382·4) requires: C, 50·25; H, 5·80%).

The identity with *trans–trans*-1-decalin-carboxylic acid was proved by mixed m.p. of the amide, acetylamino- and benzoylamino-derivative, with authentic samples.[31]

Acknowledgements—We wish to thank Professor W. G. Dauben from California University U.S.A., for the mixed m.p. of derivatives of the acid obtained from decalin, Professor C. D. Gutsche from Washington University, Saint Louis, U.S.A., for mixed m.p. and I.R. spectra of derivatives of the lower ketone obtained from decalin, and Dr. J. A. Mills from Adelaide University, Australia, for samples of derivatives of methyl-cyclohexanecarboxylic acids.

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[35] W. G. Dauben and R. C. Tweit, *J. Amer. Chem. Soc.* **76**, 3147 (1954).
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Tetrahedron, 1960, Vol. 10, pp. 65 to 70. Pergamon Press Ltd. Printed in Northern Ireland

VOL.
10
1960

CYCLOPROPENES FROM CARBENES AND ACETYLENES

STEREO-SELECTIVITY IN THE REACTION OF CARBOMETHOXYCARBENE WITH *CIS*-BUTENE

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(*Received* 1 *February* 1960)

Abstract—The addition of methylene and carbomethoxycarbene (generated photolytically from diazomethane and methyl diazoacetate, respectively) to butyne-2 gives 1,2-dimethylcyclopropene and methyl 1,2-dimethylcyclopropene-3-carboxylate, respectively. In identifying the hydrogenation product of the latter as *cis*-1,2-dimethylcyclopropane-3(*cis*)-carboxylate, it was relevant to investigate the reaction of *cis*- and *trans*-butene with methyl diazoacetate. It could be shown that addition was by the *cis*-mode, and that addition to *cis*-butene preferentially followed the sterically favored "exo" path.

CARBENES and acetylenes reacting to yield cyclopropenes is one of the many satisfying outgrowths of the renaissance of divalent carbon. Among the published examples, the earliest, by D'yakanov and Komendantov,[1] involves the reaction of phenylmethylacetylene with ethyl diazoacetate to give ethyl 1-methyl-2-phenylcyclopropene-3-carboxylate, while those immediately following, by Breslow *et al.*[2], involve the reactions of diphenylacetylene with diazomalonic ester,[2a,c] diazoacetic ester,[2b,c] phenyldiazoacetonitrile,[2d,e] and phenyl chlorocarbene.[2f] Quite recently, Vol'pin *et al.*[3] have reported the addition of dibromocarbene to diphenylacetylene, all the more significant an observation in view of the implication[4] that acetylenes should not be sufficiently nucleophilic to react. In this paper, we report the reactions of butyne-2 with two carbenes, methylene and carbomethoxymethylene, as the first illustrations of the synthesis of purely aliphatic cyclopropenes.

The decomposition of diazomethane is carried out photochemically in the usual way[5] with the exception that some dimethyl ether is admixed with the butyne-2 to prevent this relatively high melting substance from solidifying on the cold finger. Most of the unreacted butyne-2 is removed by distillation to give a concentrate from which quite unexceptional g.l.p.c. permits separation of dimethylcyclopropene in yields up to 17 per cent of theory based on N-nitrosomethylurea. Dimethylcyclopropene can be kept without polymerization in the refrigerator and in this sense is much more stable than unsubstituted cyclopropene which cannot be stored even at −75°.[6]

[1] I. A. D'yakanov and M. I. Komendantov, *Vestnik Leningrad. Univ.* **11**, No. 22, *Ser. Fiz. i Khim.* No. 4, 166 (1956); *Chem. Abstr.* **52**, 2762[i] (1958).

[2a] R. Breslow and R. Winter, Abstracts of Papers presented at the 132nd Meeting of the Amer. Chem. Soc. p. 18P, New York, September, 1957; [b] R. Breslow and M. Battiste, *Chem. & Ind.* 1143 (1958); [c] R.Breslow, R. Winter and M. Battiste, *J. Org. Chem.* **24**, 415 (1959); [d] R. Breslow, *J. Amer. Chem. Soc.* **79**, 5318 (1957); [e] R. Breslow and C. Yuan, *J. Amer. Chem. Soc.* **80**, 5991 (1958); [f] R. Breslow, private communication.

[3] M. E. Vol'pin, Yu. D. Koreshkov and D. N. Kursanov, *Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk* 560 (1959); *Chem. Abstr.* **53**, 21799[f] (1959).

[4] W. von E. Doering and W. A. Henderson, Jr., *J. Amer. Chem. Soc.* **80**, 5274 (1958).

[5] See, for example, W. von E. Doering and H. Prinzbach, *Tetrahedron* **6**, 24 (1959).

[6] M. J. Schlatter, *J. Amer. Chem. Soc.* **63**, 1733 (1941).

Support for the structure of 1,2-dimethylcyclopropene rests on the results of catallytic hydrogenation and on the interpretation of the n.m.r. spectrum. *cis*-1,2-Dimethylcyclopropane is obtained in good yield as the major product of reaction with one molar equivalent of hydrogen.[7] The minor products are n- and isopentane, easily separated in about equal amount by g.l.p.c. The n.m.r. spectrum of the olefin shows two absorptions at 198 and 245 cps in the approximate ratio, 3 : 1. Of the three possible structural isomers which could lead to 1,2-dimethylcyclopropane on hydrogenation, 1,2-dimethylcyclopropene alone would show methyl and cyclopropyl but no vinyl hydrogen in its n.m.r. spectrum. The mass spectrum confirms the molecular weight by having no mass numbers higher than 68. The most intense peak has the mass number, 67, of the parent minus one and may correspond to the 1,2-dimethylcyclopropenium ion, formed in greatest abundance by virtue of its special aromatic character.

In the infrared spectrum of 1,2-dimethylcyclopropene, the absence of any band in the 11·2 μ region where methylenecyclopropane absorbs strongly[8] is further evidence against an exocyclic methylene group. The weak absorption at 5·27 μ (CCl_4) is a point of obvious interest in the light of the anticipation by Faure and Smith[9] that the carbon–carbon double bond stretching frequency of cyclopropene should lie between those of simple olefins and acetylenes and of their actual finding that sterculic acid has a weak absorption at 5·35 μ (CS_2). There is no absorption in the ultraviolet.

The reaction of butyne-2 and methyl diazoacetate in the presence of light leads to methyl 1,2-dimethylcyclopropene-3-carboxylate (Chart 1, A). This molecule shows no absorption in the ultraviolet, has the required elementary analysis and an infrared spectrum which, lacking strong absorption at 3·23 and 11·2 μ, precludes the presence of exocyclic methylene. Catalytic hydrogenation affords a dihydro-derivative to which the structure, methyl *cis*-1,2-dimethyl-3(*cis*)-carboxylate (Chart 1, α), is assigned in the sequel.

The same α-ester is the minor product of both the photochemical and copper-catalyzed reactions of *cis*-butene with methyl diazoacetate; the major product (5 : 2) is methyl *cis*-1,2-dimethylcyclopropane-3(*trans*)-carboxylate (Chart 1, β). *trans*-Butene leads exclusively to a third product, methyl *trans*-1,2-dimethylcyclopropane-3-carboxylate (Chart 1, γ).

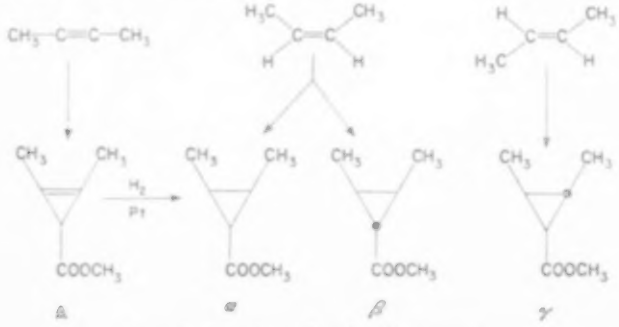

Chart 1. Reactions of methyl diazoacetate.

[7] The infrared spectrum of this material is identical with that of the sample previously considered to be *cis*-1, 2-dimethylcyclopropane: W. von E. Doering and P. LaFlamme, *J. Amer. Chem. Soc.* **78**, 5447 (1956).
[8] J. T. Gragson, R. W. Greenlee, J. M. Derfer and C. E. Boord, *J. Amer. Chem. Soc.* **75**, 3344 (1953).
[9] P. K. Faure and J. C. Smith, *J. Chem. Soc.* 1818 (1956).

On the assumption of stereospecific addition (logically, it is irrelevant whether *cis* or *trans*), of *cis* and *trans*-butene, one will give two stereoisomeric products and the other only one. This latter product, formed either by *trans*-addition to *cis*-butene or *cis*-addition to *trans*-butene, must have the *trans*-structure. In fact, the *single* product is

INFRARED SPECTRA IN CARBON TETRACHLORIDE

A[a]		α[b]		β[c]		γ[d]	
μ	ε_r	μ	ε_r	μ	ε_r	μ	ε_r
3·36	10	3·38	10	3·40	10	3·39	10
5·71	55	5·74	60	5·75	80	5·74	55
6·77	10	6·82	9	6·83	15		
6·89	35	6·92	30	6·92	35	6·91	25
7·11	20	7·16	15	7·18	8	7·20	10
7·23	30	7·26	25	7·26	8	7·33	25
				7·56	35	7·68	15
				7·89	15	7·88	7
				8·13	15		
8·33	30	8·37	30	8·36	35	8·37	35
				8·50	60	8·49	50
8·59	90	8·63	95			8·58	50
8·94	90	8·97	8	8·86	10		
9·12	20	9·15	20	9·19	15	9·11	10
				9·42	6	9·44	10
9·72	8	9·75	6	9·60	8	9·72	6
				10·20	1	10·34	4
10·58	3			10·55	3	10·61	4
10·89	4	10·68	1	10·77	8	10·82	7
		11·06	2				
11·73	8	11·75	7			11·65	5
						12·13	8
14·08	8	14·12	7	14·18	7	14·71	3

[a] Methyl 1, 2-dimethylcyclopropene-3-carboxylate. [b] Methyl *cis*-1, 2-dimethylcyclopropane-3(*cis*)-carboxylate. [c] Methyl *cis*-1, 2-dimethylcyclopropane-3(*trans*)-carboxylate. [d] Methyl *trans*-1, 2-dimethylcyclopropane-3-carboxylate.

obtained from *trans*-butene and is therefore methyl *trans*-1,2-dimethylcyclopropane-3-carboxylate (Chart 1,γ). It follows that the mode of addition to the olefin must have been *cis*. Further justification for the assumption of stereospecific addition is to be found in the fact that there is no overlapping of products from *cis* and *trans*-butene—the former giving the *two* (and therefore *cis*) 1,2-dimethylcyclopropane-3-carboxylates, α and β, the latter the *single*, *trans* isomer, γ.[10]

Structural distinction between the α and β *cis*-esters can be made by uncomplicated application of the principle of surface hindrance in catalytic hydrogenation.[11]

[10] It is presumably by some such argument as this that the following, otherwise undocumented statements by P. S. Skell and R. C. Woodworth, *J. Amer. Chem. Soc.* **78**, 4496 (1956) find partial justification: "The criterion of stereospecific addition to the 2-butenes has been used to detect other carbene reaction intermediates. For example, photolyses of ethyl diazoacetate in the presence of these olefins produces carbethoxycarbene, $:CHCOOC_2H_5$, since the ethyl 2,3-dimethylcyclopropane carboxylates are obtained in stereospecific reactions. Copper-bronze catalysis produces the same results as photolysis."

[11] R. P. Linstead, W. von E. Doering, S. B. Davis, P. Levine and R. R. Whetstone, *J. Amer. Chem. Soc.* **64**, 1985 (1942).

Addition of hydrogen being from the catalyst surface to the under side of the absorbed olefin in *cis* fashion, the geometry of adsorption controls the stereochemistry of the product. In the case of methyl 1,2-dimethylcyclopropene-3-carboxylate, the favored conformation of adsorption leaves the methyl carboxylate group *trans* to the catalyst surface and leads to an all-*cis* product. Accordingly, the α-isomer is the methyl *cis*-1,2-dimethylcyclopropane-3(*cis*)-carboxylate and, by default, the β-isomer is the methyl *cis*-1,2-dimethylcyclopropane-3(*trans*)-carboxylate.

Parenthetically, it is noteworthy that the addition of carbomethoxy carbene to *cis*-butene is the only example in which, with *cis*-addition demonstrated, a second stereochemical choice, analogous to the *endo-exo* choice in the Diels–Alder reaction, is open to the reactants. Whereas the *endo* choice is overwhelmingly preferred in all but a few examples of the Diels–Alder, in the addition of this carbene no striking discrimination is shown. What little there is seems to be sterically controlled and corresponds in the Diels–Alder analogy to *exo*-addition. With *cis*-addition being indicated, the examples of Wilberg *et al.*[12] in which the additions of carboethoxycarbene to ethyl acrylate, vinyl bromide and vinyl *t*-butyl ether give *trans*-products, now become further illustrations of the steric favoring of *exo*-addition.

We hope to exploit the more ready availability of simple cyclopropenes by studying the chemistry of the ring system in greater detail than has heretofore been conveniently possible.

EXPERIMENTAL

1,2-*Dimethylcyclopropene*

A solution of diazomethane in decalin was prepared by adding 4·8 g N-methyl-N-nitrosourea to a well-stirred, ice-cold mixture of 40 ml decalin and 30 ml 45% aqueous potassium hydroxide over a period of 10 min. One quarter of the solution of diazomethane in decalin (at −70°) was transferred to a test-tube which was connected through a cork stopper and T-tube to two stopcocks: one leading to the top of the irradiation vessel—a simple, transparent Dewar-type of cold finger with an elongated outer wall, the inner wall serving as a dry-ice condenser—and a 1 l. reservoir; the other, to a vacuum pump. The diazomethane was transferred to the chilled (−70°) solution of 18 ml butyne-2 and 5 ml dimethyl ether in the Dewar vessel by evacuating the 1-l. bulb and allowing the decalin solution to warm to room temp. During irradiation, the upper part of the Dewar flask is protected by a jacket of aluminum foil and illumination is from below by two 275 watt General Electric Sunlamps. A total of eight doses of diazomethane was introduced at intervals sufficiently long to permit the decomposition of the preceding dose.

The reaction product was distilled, material boiling below 45° being collected. Analysis of the mixture by g.l.p.c. using a 2-m tetraisobutylene column (D) in a Perkin–Elmer 154 Fractometer operated at 26° and with helium at 10 lb/in² indicated 7·5% of the 1,2-dimethylcyclopropene corresponding to 17% of theory based on N-methyl-N-nitrosourea. On this column the retention time of butyne-2 is 10 min and that of dimethylcyclopropene is 16 min. Larger quantities of product were separated by distilling most of the butyne-2 in an 18″ helix-packed column and then passing many 100 mg samples of the concentrate through the 1/4″ g.l.p.c. column. Collection was accomplished in the usual manner in a U-tube surrounded by dry-ice. It was also possible to effect purification (>90%) on a 4′ g.l.p.c. column, 2″ in diameter, packed with didecylphthalate on firebrick.

1,2-Dimethylcyclopropene is a colorless, moderately stable liquid of f.p. −35 to −33° and having a vapor pressure of 150 mm at 0° (corresponding to a b.p. of about 40°). It polymerizes slowly at room temp and is easily stored at 4°. There is no maximum absorption in the U.V. above 215 mμ nor any absorption with log $\varepsilon > 1$ above 230 mμ (10^{-3} M solution in ethanol). The n.m.r. spectrum measured in a Varian Associates Model 4300 V at 40·01 mc with superstabilizer and spinning sample, showed two peaks, one at 198 ± 3, the other at 245 ± 3 c.p.s. (relative to the phenyl hydrogen of toluene) in an approximate ratio of 3:1. The gas-phase (10 mm pressure in an 8·5 cm cell) infrared

[12] K. B. Wiberg, R. K. Barnes and J. Albin, *J. Amer. Chem. Soc.* **79**, 4994 (1957); E. N. Trachtenberg and G. Odion, *Ibid.* **80**, 4015 (1958); G. L. Closs and L. E. Closs, *Ibid.* **81**, 4996 (1959).

is comparatively simple. Omitting several very weak transitions, the spectrum seems to consist of the following bands: sharply separated, strong doublet at 3·43 and 3·52 μ; a weak peak at 5·27; weak peak at 6·70, moderate peak at 6·91, a poorly resolved doublet at 8·42 and 8·50 and a strong triplet at 9·78, 9·86 and 9·95 μ, with the central peak being exceedingly sharp. The spectrum in carbon tetrachloride (5%) follows: 3·44 (S); 3·52 (S); 5·29 (W); 5·81 (VW); 5·92 (VW); 6·75 (M); 6·93 (S); 8·46 (M); 8·63 (M); 9·91 (S).

The molecular weight was established by the mass spectral cracking pattern which shows no masses above the parent 68 (with the exception of the ^{13}C isotope mass at 69). The mass spectrum at 70 V. is given here along with intensities relative to that of mass 67 as 100: 69 (5·0), 68 (92·6) 67 (100·0), 66 (10·5), 65 (15·1), 63 (5·0), 62 (4·4), 61 (3·4), 60 (0·7), 54 (3·2), 53 (63·1), 52 (7·8), 51(16·7), 50 (11·7), 49 (2·5), 44 (CO_2, 1·2), 43 (1·1), 42 (14·6), 41 (75·6), 40 (31·2), 39 (57·6), 38 (9·5), 37 (5·2), 36 (0·5), 32 (O_2, 1·4), 31·5 (1·4), 31 (6·1), 29 (3·2), 28 (N_2, 5·1), 27 (49·3), 26 (5·1), 25 (0·5), 15 (2·2).

Catalytic hydrogenation of 1,2-*dimethylcyclopropene*

In a vacuum-line system about 30 mg (20 cm mercury in the system employed) dimethylcyclopropene was condensed into 0·25 ml iso-octane containing 5 mg pre-reduced platinum oxide catalyst. Under 500 mm press of hydrogen, the cyclopropene was reduced at about 0° with magnetic stirring. Diffusion of the cyclopropene throughout the vacuum system was minimized by the appropriate use of stopcocks and by condensing the volatile materials back into the iso-octane solution by periodic cooling with dry-ice.

After uptake of hydrogen had ceased (a fall in pressure of 21 cm mercury), the hydrogenation product was condensed and chromatographed on a 2 m dioctylphthalate column at 25–26° with helium at 10 lb/in².

The most abundant product amounted to 70% of the volatile materials, and had the same retention time (about 16 min), mass spectrum and infrared spectrum as that of a sample of authentic *cis*-1,2-dimethylcyclopropane.[7]

The rest of the product consisted of two substances in roughly equal quantity having retention times of 10 and 7·5 min and being identified by mass spectroscopy as n-pentane and isopentane, respectively.

Methyl 1,2-*dimethylcyclopropene*-3-*carboxylate*

A mixture of 23 g butyne-2, 7 g methyl diazoacetate and 25 g isobutane (used as solvent to prevent the butyne-2 from crystallizing on the cold finger) was placed in a flask fitted with a condenser of the cold finger type filled with dry ice. At the end of 30 hr irradiation with three 275 watt General Electric sunlamps, the diazoacetic ester was decomposed. Distillation afforded 3·5 g material, b.p. 45–60° at 2 mm. Separation by g.l.p.c. (Perkin–Elmer Fractometer 154; 4 m didecylphthalate column at 130°) afforded pure methyl 1,2-dimethylcyclopropene-3-carboxylate as the major component (80%) in 32% of theoretical yield; n_D^{20} 1·4412 (Found: C, 66·4; H, 8·2. $C_7H_{10}O_2$ requires: C, 66·7; H, 8·0%).

Catalytic hydrogenation of methyl 1,2-*dimethylcyclopropene*-3-*carboxylate*

The crude (80%) reaction product (0·5 g) was hydrogenated over platinum oxide in ethyl acetate at room temp and atm. press. The crude product was analysed by g.l.p.c. (4-m didecylphthalate column at 125° and helium at 25 lb/in²). At least 70% of the product had the same retention time and same infrared spectrum as the α-isomer, methyl *cis*-1,2-dimethylcyclopropane-3(*cis*)-carboxylate, obtained below from *cis*-butene and methyl diazoacetate. There was no detectable amount of any other stereoisomer.

Photochemical reaction of methyl diazoacetate with cis-butene

After being irradiated for 40 hr with three 275-watt General Electric sunlamps, a solution of 8 g methyl diazoacetate in 40 ml *cis*-butene had become colorless. Distillation afforded 4·0 g (39% of theory) material, b.p. 50–60° at 50 mm. In g.l.p.c. on a 4-m didecylphthalate column at 130° and 25 lb/in² of helium, the product consisted of a mixture mainly of two substances, α (r.t. 42 min; n_D^{20} 1·4308. Found: C, 65·5; H, 9·5. $C_7H_{12}O_2$ requires: C, 65·6; H, 9·4%) and β (r.t. 47 min; n_D^{20} 1·4306. Found: C, 65·5, H, 9·7. $C_7H_{12}O_2$ requires: C, 65·6; H, 9·4%) with small quantities

of at least four other substances of shorter retention time. The ratio of α to β was about 2:5. Both isomers were stable to neutral permanganate solution.

The α-isomer was not rearranged appreciably to the β by treating with methanolic sodium methoxide for 6 hr at 60°.

The copper catalyzed reaction of methyl diazoacetate with cis-*butene*

This reaction was effected by adding gradually, at such a rate as to maintain a steady evolution of nitrogen, 3·0 g methyl diazoacetate and 2·5 g anhydrous copper sulfate to 20 ml *cis*-butene. Filtered and freed of volatile material, the product consisted largely of crystalline dimethyl fumarate with a small amount (5–10%) of the same mixture (2:5) of isomers α and β as above.

Photochemical reaction of methyl diazoacetate with trans-*butene*

In the same manner as above, 8·0 g methyl diazoacetate was irradiated in 50 ml *trans*-butene. Distillation afforded 3·5 g (34% of theory) material; b.p. 40–50° at 20 mm; n_D^{20} 1·4252. The major product, methyl *trans*-1,2-dimethylcyclopropane-3-carboxylate (Found: C, 65·3; H, 9·3. $C_7H_{12}O_2$ requires: C, 65·6; H, 9·4%), had a retention time of 33 min at 126° and at a helium pressure of 25 lb/in² in the same column as that used in the *cis*-butene experiment.

Infrared spectra

The spectra were measured in carbon tetrachloride solution in a 0·01 cm cell in a Perkin–Elmer Model 21 Infrared Spectrometer. Included in the tabulation of the spectra is a rough measure of intensity obtained from the optical densities by dividing by the product of the cell thickness (0·01 cm) and the concentration expressed in moles per 1000 g of carbon tetrachloride. The resulting "extinction coefficients" were normalized (ε_r) by taking the value 10 for the carbon–hydrogen stretching band.

Tetrahedron, 1960, Vol. 10, pp. 71 to 75. Pergamon Press Ltd. Printed in Northern Ireland

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THE STEREOCHEMISTRY OF MANOYL OXIDE

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(*Received* 15 *February* 1960)

Abstract—The stereochemistry of manoyl oxide at C_8 has been established by hydrogenolysis to 8α-hydroxylabd-13-ene. Electron-impact induced fission of the molecule shows that C_{16} has a β-configuration, and hence manoyl oxide is represented by I.

THE tetrahydropyran ring in dihydromanoyl oxide has been opened[1] to give a dichloride which has been obtained from sclareol; but no valid deductions can be made about the stereochemistry at C_8 and C_{13} in manoyl oxide.

Ohloff has shown[2] that a manoyl oxide can be prepared from sclareol. This synthetic material has m.p. 94–96°, $[\alpha]_D$ +37·5°, while natural manoyl oxide has m.p. 24·5–26°, $[\alpha]_D$ +23°. He suggested that either natural manoyl oxide was impure or that the synthetic material was an isomer at C_8 or C_9. Natural manoyl oxide behaves as a pure substance during gas–liquid chromatography with a retention time of 22·9 min at 195° on a column of 5 per cent Apiezon L on 120 mesh celite. A sample of the synthetic material, with m.p. 94–96°, showed two peaks with *rT*'s of 22·9 and 24·9 min. The first of these was inseparable from natural manoyl oxide by this technique and amounted to approx 2 per cent of the synthetic sample.

It is clear that the bulk of the synthetic oxide must be a stereoisomer of natural manoyl oxide, and will be designated as epi-manoyl oxide. It is probable that during the cyclization of sclareol the oxide ring in epi-manoyl oxide will be attached to C_8 from the α-face of the molecule. As is shown later, this is the configuration at C_8 in manoyl oxide, so it seemed likely that the material prepared by Ohloff was a C_{13} epimer. This was shown to be so, by hydrogenolysis of both epimers to give the same 8α-hydroxylabd-13-ene (II).

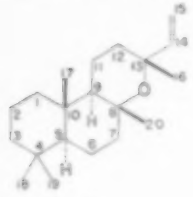
Dehydration of II with phosphorus oxychloride in pyridine produced an inseparable mixture of three products in the ratio of 75 : 16 : 9 (determined by gas–liquid chromatography). It would appear that all three possible dehydration products have been formed. That the major component was labda-8(20),13-diene was demonstrated by a quantitative comparison of the infra-red spectrum of the mixture with that of α-onocerin diacetate. The ΔM_D (olefin-alcohol) for the mixture had a value of +105 which is in reasonable agreement with that of +98° between sclareol and manool. Since this rotation difference corresponds to the removal of one asymmetric centre, it is probable that C_{20} in manoyl oxide has a β orientation.

Hydroxylation of manoyl oxide, followed by oxidation with lead tetracetate gave the aldehyde (IIIa). When this was oxidized with chromium trioxide, two products were formed; the lactone (IV) and the acid (IIIb). Since IV is known[3] to be less stable than the corresponding 8-epimer, its isolation from this reaction is further

[1] J. R. Hosking and C. W. Brandt, *Ber. Dtsch. Chem. Ges.* **68**, 37 (1935).
[2] G. Ohloff, *Liebigs Ann.* **617**, 134 (1958).
[3] M. Hinder and M. Stoll, *Helv. Chim. Acta* **36**, 1995 (1953).

evidence of an 8α-oxido group in manoyl oxide. The sodium salt of the acid was treated with oxalyl chloride, followed by conversion to the diazoketone and heating with cupric oxide in toluene.[4] It was thought that, if the carboxyl group in IIIb was *cis* with respect to C_{20}, cyclization to V may take place. However, no pure ketonic material was isolated.

It was then decided to alter the shape of the manoyl oxide molecule in such a way



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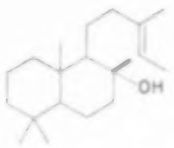

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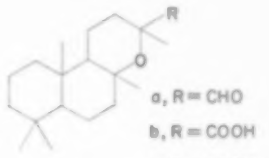

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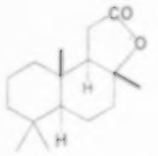

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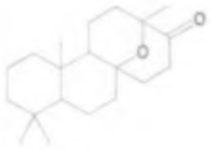

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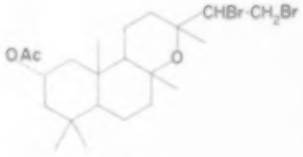

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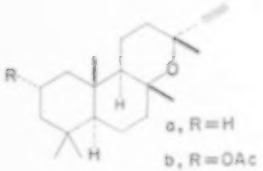
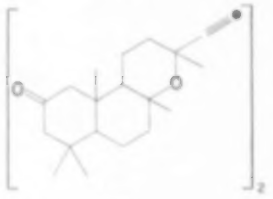
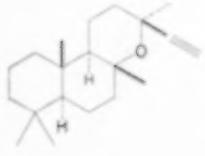


VII

VIII



IX



X

that it should be distinguishable from its C_{13} epimer. 2-Oxomanoyl oxide was reduced with sodium borohydride, the alcohol acetylated and the product brominated giving 2α-acetoxy-14,15-dibromo-8α,13-oxido-labdane (VI). This was dehydrobrominated to the 2-acetoxyacetylene (VIIb) which was converted to the ketone (VIII).

This was oxidatively dimerized to 15,15′-di(8α,13-oxido-2-oxolabd-14-ynyl) (IX). Though the two C_{13} epimers of this structure have very different molecular dimensions no steric conclusions could be drawn from an X-ray determination of the size of the crystal unit cell of IX.

[4] F. Greuter, J. Kalvoda and O. Jeger, *Proc. Chem. Soc.* 349 (1958).

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The acid (IIIb) has infra-red absorption at 3360 cm^{-1} and 1780 cm^{-1} in dilute carbon tetrachloride solution, showing strong intramolecular hydrogen bonding. This bonding must be between the hydrogen of the carboxyl group and the ether oxygen, involving a five-membered ring, which may contribute towards the abnormally high frequency of the carbonyl absorption. In addition, this frequency would be increased by the presence of an α-oxygen substituent. The methyl ester IIIc showed two bands at 1731 and 1751 cm^{-1} comparable with those reported for many α-halogenoesters and for allyl phenoxyacetate.[5] It would appear, from models, that bonding of this type would be unlikely in a structure with a β-carboxyl group unless the tetrahydropyran ring was in a boat form. Hence it is probable that IIIb has an α-carboxyl group. Unfortunately, through lack of material, we were unable to confirm this by preparing the 13-epimer of IIIb. However, conclusive evidence on this point was obtained by electron-impact induced fission of manoyl oxide, which is discussed below.

Evidence has accumulated which suggests that the break-down of the molecular ions of epimeric compounds differs.[6] This gives rise to "cracking-patterns" which differ in the intensity of the fragment ions, rather than in the ion species formed. These differences in intensity have been interpreted in terms of the congestion of the molecular structure around the centres of cleavage.

Accordingly, an examination of the cracking-patterns of manoyl oxide and epimanoyl oxide was made. The relative ease of loss of a methyl group from both systems was compared. Clearly, because of the presence of five methyl groups in each molecule, the contribution to ions of mass 15, and of mass 275 representing the parent minus 15 (P-15), may be made up from fissions from any of these centres. The relative ease of loss of a methyl group from all positions except C_8 and C_{13} may be expected to be very nearly the same and consequently any inequality occuring in the intensities of the fragment ions mentioned may be attributed to the differing ease of loss of methyl groups at these centres. Experiment shows that there is proportionally greater loss from manoyl oxide than epimanoyl oxide suggesting that the substitutents on the oxide-ring are in a more congested environment in the former.

Since it is known that allylic bonds are very susceptible to fission,[7] experiments were carried out in which the electron beam energy was in the region of the appearance potential of the ion obtained by the loss of a methyl group from the parent molecular ion. Comparison of the ratio of the intensities P-15/P were made, giving ratios which varied slightly with the accelerating voltage, but were of the order of ·46 and ·35 for manoyl oxide and epimanoyl oxide respectively. Notwithstanding the variations with ionizing potential, the ratio for manoyl oxide was always the greater under the same bombardment conditions. This confirms the observation that the groups are in the more congested position in manoyl oxide.

Some ambiguity remains; as the configuration around C_{13}, which bears both the methyl and vinyl group, will depend upon which group exerts the greatest steric congestion in the β-configuration. Hence, similar experiments were conducted upon the corresponding compounds in which the vinyl group was replaced by an acetylene residue. In this series the interaction of an 8β-methyl group with a 13β-ethynyl group

[5] M. L. Josien and C. Castinel, *Bull. Soc. Chim. Fr.* 801 (1958).
[6] K. Bjemann and J. Seibl, *J. Amer. Chem. Soc.* **81**, 3149 (1959).
[7] R. A. Brown and E. Gillams, A.S.T.M. Committee E-14 on Mass Spectrometry, 2nd Annual Meeting, New Orleans (1954).

must certainly be less than that with a 13β-methyl. The intensity of the parent molecular ion was rather low, but a comparison was made between the fragment ions of mass 273 and 263 corresponding to the loss of a methyl and an ethynyl group respectively. For 8α,13-oxidolabd-14-yne (VIIa) the ratio of intensity of the ions is 3·10 which is greater than 1·97 for 8α,13-epioxidolabd-14-yne (X). This indicates a preferential loss of a methyl group in the acetylenic derivative having the same conformation as manoyl oxide. A check upon this deduction was made by examining the relative intensities of the two ions, methyl and ethynyl, which gave the same result. Finally a low energy analysis of P-15/P for both these compounds supported this conclusion. Consequently one may deduce that in manoyl oxide, C_{16} is in the axial β-position which is the more congested one. Though, of necessity, the 8α,13-epioxidolabd-14-yne was not available in sufficient quantity for elemental analysis, there can be no doubt as to the validity of this conclusion.

It has been assumed that the tetrahydropyran ring in manoyl oxide and its derivatives is in a chair form. Should this not be so, the interpretation of the "cracking-patterns" becomes difficult, but it would seem likely that manoyl oxide has C_{16} in an α-configuration.

EXPERIMENTAL

Rotations were measured in chloroform at room temp unless otherwise stated. M.p.'s were taken on a Kofler block and are corrected. The alumina used for chromatography had activity III. Light petroleum refers to the fraction with b.p. 60–80°.

8α-*Hydroxylabd*-13-*ene* (II). 8α,13-Oxidolabd-14-ene (I, manoyl oxide, 500 mg) in ether (15 ml) was added to a solution of lithium (1 g) in liquid ammonia (75 ml). After 30 min the excess lithium was destroyed with ammonium chloride and the product adsorbed on alumina (50 g) from light petroleum. Elution with benzene–ether (9:1) gave II as needles (445 mg) from aqueous methanol, m.p. 99–100·5°, $[\alpha]_D$ −1° (*c*, 1·0). (Found: C, 82·1; H, 12·4. $C_{20}H_{36}O$ requires: C, 82·1; H, 12·4%). Infra-red absorption in Nujol at 826 cm^{-1} (—CH—C). Hydrogenolysis of epi-manoyl oxide under the same conditions gave the same product. Reaction of II, in acetic acid, with ozonized oxygen gave acetaldehyde, isolated as its 2,4-dinitrophenylhydrazone in 63% yield.

Dehydration of 8α-*hydroxylabd*-13-*ene*. 8α-Hydroxylabd-13-ene (93 mg), phosphorus oxychloride (200 ml) and pyridine (2 ml) were maintained at 20° for 15 hr. The product, in pentane was filtered through alumina (activity I) and distilled at 100°/0·05 mm, $[\alpha]_D$ +37·3° (*c*, 1·3). (Found: C, 87·9; H, 12·2. $C_{20}H_{34}$ requires: C, 87·5; H, 12·5%).

Oxidation of manoyl oxide. Manoyl oxide (1·31 g), osmium tetroxide (1·25 g) and pyridine (5 ml) were allowed to react in ether at 0° for 48 hr. The resulting osmate ester was decomposed with hydrogen sulphide. The product was adsorbed on alumina (100 g) from benzene and eluted with ether–methanol (19:1) as a black oil (1·35 g). This was heated under reflux for 30 min with lead tetracetate (3·5 g) in benzene (60 ml), adsorbed from benzene on alumina and the aldehyde (IIIa) eluted with benzene–ether (9:1) as a colourless oil (390 mg). This was characterized as its semicarbazide which crystallized as fine needles from aqueous ethanol, m.p. 225–227·5°. (Found: C, 68·45; H, 10·15; N, 11·85. $C_{20}H_{35}O_2N_3$ requires: C, 68·75; H, 10·1; N, 12·0%). (Lit.[2], m.p. of the 13-epimer: 210–212°).

Oxidation of the aldehyde (IIIa). IIIa (169 mg) and chromium trioxide (39 mg) were allowed to react in acetic acid (5 ml) for 12 hr at 20°. The acidic product was adsorbed on silica gel (20 g) from benzene and eluted with chloroform as needles (72 mg from aqueous methanol) of the acid (IIIb), m.p. 45–47°, m.p. 97–98° after drying for 48 hr at 40°/0·05 mm, $[\alpha]_D$ +42° (*c*, 0·7). (Found: C, 74·4; H, 10·3. $C_{19}H_{32}O_3$ requires: C, 74·0; H, 10·45%).

Methylation of IIIb with ethereal diazomethane gave the ester (IIIc) as needles from aqueous methanol, m.p. 83–85°, $[\alpha]_D$ +14° (*c*, 0·5). (Found: C, 74·65; H, 10·7. $C_{20}H_{34}O_3$ requires: C, 74·5; H, 10·65%). Infra-red absorption in CCl_4 at 1731 and 1751 cm^{-1}).

The neutral product from the chromium trioxide oxidation was adsorbed on alumina (20 g) from light petroleum and eluted with benzene–ether (9:1) as flat needles (21 mg from light petroleum) of

the lactone (IV), m.p. 125–126·5°, $[\alpha]_D$ +41° (*c*, 0·8 in benzene). (Lit.[8] values: m.p. 125°, $[\alpha]_D$ +41°). (Found: C, 77·0; H, 10·05. $C_{16}H_{26}O_2$ requires: C, 76·75; H, 10·45%). The infra-red spectrum in nujol was identical with that published in the literature.

2α-*Acetoxy*-8α,13-*oxidolabd*-14-*ene*. 8α,13-Oxido-2-oxolabd-14-ene (2-oxomanoyl oxide, 250 mg) was treated with sodium borohydride (250 mg) in aqueous methanol (15 ml) for 2 hr. The crude product was heated under reflux for 1 hr with acetic anhydride (4 ml) and sodium acetate (500 mg), then adsorbed on alimina (25 g) from light petroleum and eluted with light petroleum–benzene (9:1) as prisms of 2α-*acetoxy*-8α,13-*oxidolabd*-14-*ene* (200 mg) from light petroleum, m.p. 107·5–109°, $[\alpha]_D$ +37° (*c*, 1·5). (Found: C, 75·8; H, 10·45. $C_{22}H_{36}O_3$ requires: C, 75·8; H, 10·4%).

2α-*Acetoxy*-14,15-*dibromo*-8α,13-*oxidolabdane* (VI). 2α-Acetoxy-8α,13-oxidolabd-14-ene (54 mg) in carbon tetrachloride (3 ml) was treated with bromine (0·85 ml, 2·9% soln. in CCl_4) at 0°. When the reaction was complete the solution was washed with sodium bicarbonate. Removal of the solvent gave the dibromide (VI) as prisms (48 mg) from light petroleum, m.p. 125–134°. (Found: C, 52·95; H, 7·0. $C_{22}H_{36}O_3Br_2$ requires: C, 52·0; H, 7·15%).

2α-*Hydroxy*-8α,13-*oxidolabd*-14-yne (VIIc). The dibromide (VI, 950 mg) in ether (20 ml) was stirred for 3 hr with a suspension of sodamide (from 2 g Na) in liquid ammonia (100 ml) at −33°. After reacetylation, the product was adsorbed on alumina (100 g, grade V) from light petroleum and eluted with light petroleum–benzene (9:1) as prisms (370 mg from light petroleum) of 2α-*acetoxy*-8α,13-*oxidolabd*-14-*yne* (VIIb), m.p. 115–116·5°, $[\alpha]_D$ +12° (*c*, 1·2). (Found: C, 76·4; H, 10·0. $C_{22}H_{34}O_3$ requires: C, 76·25; H, 9·9%). Hydrolysis of VIIb gave the corresponding alcohol (VIIc) as prisms from light petroleum, m.p. 104–105°, $[\alpha]_D$ +38° (*c*, 0·8). (Found: C, 78·7; H, 11·1. $C_{20}H_{32}O_2$ requires: C, 78·9; H, 10·6%).

8α,13-*Oxido*-2-*oxolabd*-14-*yne* (VIII). Oxidation of VIIc (125 mg) in acetone (10 ml) with 8N chromic acid/sulphuric acid gave VIII (112 mg) as prisms from light petroleum, m.p. 98–100°, $[\alpha]_D$ +29° (*c*, 0·9). (Found: C, 79·7; H, 10·0. $C_{20}H_{30}O_2$ requires: C, 79·4; H, 10·0%).

15,15′-*Di*(8α,13-*oxido*-2-*oxolabd*-14-*ynyl*) (IX). 8α,13-Oxido-2-oxolabd-14-yne (92 mg), cupric acetate (200 mg) and pyridine (2 ml) were heated together under reflux for 20 min. The product crystallized as needles of IX (78 mg) from methylene chloride–methanol, m.p. 258–260°, $[\alpha]_D$ − 40° (*c*, 0·65). (Found: C, 79·5; H, 9·95. $C_{40}H_{58}O_4$ requires: C, 79·7; H, 9·7%). $\lambda_{max}(CH_2Cl_2)$ 232, 243, 254, 284 mμ; ε = 405, 410, 310, 136.

8α,13-*Oxidolabd*-14-*yne* (VIIa). Manoyl oxide (25 mg) was converted to the corresponding acetylene (VIIa) by the method described for the preparation of VIIb. Distillation at 130°/0·1 mm gave VIIa (10 mg) as a colourless oil, $[\alpha]_D$ +7° (*c*, 1·2). (Found: C, 83·05; H, 11·45. $C_{20}H_{32}O$ requires: C, 83·25; H, 11·2%).

8α,13-*Epioxidolabd*-14-*yne* (X). Epimanoyl oxide (2·5 mg) gave X (0·5 mg), subliming as prisms, m.p. 99–102°.

The electron impact studies were carried out on a Metropolitan Vickers Ltd. M.S.2. Mass-spectrometer. The "cracking-patterns" were obtained in the conventional way using an ion accelerating voltage of 2 kV with an electron beam energy of 50 eV. The appearance potentials were obtained by known methods.[9]

Acknowledgements—The author thanks Dr. P. K. Grant for a generous gift of 2-oxo-manoyl oxide, Dr. G. Ohloff for a sample of epi-manoyl oxide, J. M. Wilson for assistance with mass-spectrographic measurements and Professor R. A. Raphael for his advice and encouragement.

[8] R. J. Reed, *Trans. Faraday Soc.* **52**, 1195 (1956).

Tetrahedron, 1960, Vol. 10, pp. 76 to 80. Pergamon Press Ltd. Printed in Northern Ireland

FREE-RADICAL REACTIONS INVOLVING SULPHUR COMPOUNDS—III

PHOTOLYSIS OF AROMATIC DISULPHIDES

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(*Received* 1 *March* 1960)

Abstract—Dimesityl disulphide (MS–SM) proved to be a particular suitable model compound for investigating the photo-dissociation reaction of aromatic disulphides. The rate and mechanism of the photo-dissociation of MS–SM in the presence of an active hydrogen donor such as 9,10-dihydroanthracene was studied in a plurality of solvents. Generally, rate constants were found to decrease with increasing kinematic viscosity of the solvent.

IN the formation of thiols upon irradiation of solutions of disulphides,[1] the solvent is generally thought to function as the hydrogen donor.[2] It has now been found, however, that thiols are also formed on irradiation of solutions of diphenyl disulphide *in hydrogen-free solvents*,[3] their amount increasing with time (Table 1). The formation of thiophenol could not be detected in the dark, however, even in the presence of an active hydrogen donor as, for example, 9,10-dihydroanthracene.

TABLE 1. PHOTOLYSIS OF 0·06 M SOLUTIONS OF DIPHENYL DISULPHIDE AT 25°, IN A NITROGEN ATMOSPHERE. STANDARDIZED IRRADIATION BY FLUORESCENT LAMPS

Solvent	Duration of irradiation (hr)	% S converted into thiol
Toluene	66	16
Dimethyl phthalate	66	16
Carbon tetrachloride	66	9
Tetrachloro ethene	66	8
Toluene	18	7
Toluene	42	13
Toluene	66	17
Toluene	90	22
Toluene	70	18·4[a]
Paraffin oil	66	9·3[b]

[a] Mean equivalent weight of thiols formed = 170.
[b] Mean equivalent weight of thiols formed = 169.

* Present address: Leiden University.

[1] W. E. Lyons, *Nature, Lond.* **162,** 1004 (1948).
[2] C. Walling and R. Rabinowitch, *J. Amer. Chem. Soc.* **81,** 1137 (1959).
[3] See also Y. Schaafsma, *Chem. Weekblad* **54,** 61 (1958).

Presumably, a light-induced rearrangement of diphenyl disulphide occurs, for instance by the following reactions:

$$C_6H_5\text{–}S\text{–}S\text{–}C_6H_5 \xrightarrow{h\nu} 2C_6H_5\text{–}S\cdot \quad (1)$$

$$C_6H_5\text{–}S\cdot + C_6H_5\text{–}S\cdot \longrightarrow C_6H_5\text{–}S\text{–}C_6H_4\text{–}SH \quad (2)$$

$$C_6H_5\text{–}S\cdot + C_6H_5\text{–}S\text{–}C_6H_4\text{–}SH \longrightarrow C_6H_5\text{–}SH + C_6H_5\text{–}S\text{–}C_6H_4\text{–}S\cdot \quad (3)$$

$$C_6H_5\text{–}S\text{–}C_6H_4\text{–}S\cdot + C_6H_5\text{–}S\cdot \longrightarrow \text{disulphides} \quad (4)$$

This reaction scheme is supported by the mean equivalent weight of the thiols in the reaction product, which is 170, a value intermediate between 110 for thiophenol and 218 for the (*o*, *p*)-mercaptodiphenyl sulphide formed in reaction (2).

It is obvious that reactions (2), (3) and (4) interfere seriously with the following—otherwise appropriate—methods for investigating disulphide dissociation, viz. (a) photolysis in the presence of the stable free radical 1,1-diphenyl-2-picrylhydrazyl (P·),[4] which moreover reacts readily with thiols;[5] (b) photolysis in the presence of a suitable hydrogen donor.

We have succeeded in completely preventing reactions of type (2) by blocking all *ortho* and *para* positions of diphenyl disulphide by methyl groups. In dimesityl disulphide (MS–SM) therefore, we have a compound which is pre-eminently suitable for investigating the photo-dissociation of aromatic disulphides.

In the present preliminary account of our work, some reactions with this compound are reported.

(a) *The photochemical reaction of dimesityl disulphide with the stable free radical* 1,1-*diphenyl-2-picrylhydrazyl*

This reaction was thought to provide independent chemical evidence of the transient existence of free thiyl radicals.[4] The reactions occurring in this system are:

$$MS\text{–}SM \rightarrow 2MS\cdot \qquad k_1 \quad (5)$$

$$2MS\cdot \rightarrow MS\text{–}SM \qquad k_2 \quad (6)$$

$$MS\cdot + P \rightarrow \text{product} \qquad k_p \quad (7)$$

Presumably $k_2 \gg k_p$ and with the disulphide present in large excess the decay of P· is given by:

$$-\ln [P\cdot] = K \cdot t \cdot [MS\text{–}SM]^{1/2} - \ln [P_o\cdot]$$

In accordance with this equation a first order decay of [P·] is found (Table 2).

TABLE 2. REACTION OF 1,1-DIPHENYL-2-PICRYLHYDRAZYL [P·] AND DIMESITYL DISULPHIDE [MS–SM] ON IRRADIATION AT 25° IN CCl_4 SOLUTION

[P·] (mmole/l.)	[MS–SM] (mmole/l.)	Fluorescent lamps	Duration (hr)	Conversion of P·	$K\sqrt{[MS\text{–}SM]}$ s^{-1}	K $l^{1/2}s^{-1}$ $mol^{-1/2}$
0·092	7·26	(in the dark)	20	nil	—	—
0·071	—	8 × 20 Watt	2	~5%	—	—
0·064	1·26	2 × 8 Watt	2	~80%	$0{\cdot}175 \times 10^{-3}$	$4{\cdot}9 \times 10^{-3}$
0·068	5·24	2 × 8 Watt	1	~80%	$0{\cdot}33 \times 10^{-3}$	$4{\cdot}5 \times 10^{-3}$

[4] J. A. Barltrop, P. M. Hayes and M. Calvin, *J. Amer. Chem. Soc.* **76**, 4348 (1954).
[5] K. E. Russell, *J. Phys. Chem.* **58**, 437 (1954).

(b) *Hydrogen abstraction by dimesityl disulphide*

Radicals MS·, produced photolytically from MS–SM, are converted into mesitylenethiol, MSH, by reaction with a hydrogen-donor molecule, e.g., 9,10-dihydroanthracene, HAH. Depending on the ratio of MS–SM to HAH one or two hydrogen atoms may be abstracted from the latter. For instance, employing equimolar amounts, a 77·5 per cent conversion of disulphide sulphur to MSH and a 83 per cent conversion of HAH was obtained, anthracene (A) and anthracene–dimer (A–A) being the main products. By doubling the amount of HAH–other conditions being the same as in the foregoing experiment—the same yield of MSH and the same conversion of HAH were obtained, 9,9′10,10′-tetrahydrobianthryl (HA–AH) being predominantly formed. Whereas HAH and HA–AH proved to be stable towards the light used, A was converted into A–A.

The possible action of A as a photosensitizer was separately investigated by using it as an additive in an experiment with 9-methoxyfluorene as the hydrogen donor. No accelerating influence was observed, however.

HA–AH can act as a hydrogen donor as well, being converted mainly into A–A. Since in the dark the reaction of HA–AH with MS· radicals (generated from MSH by 2-cyano-2-propyl radicals[6]) produced monomeric anthracene exclusively, the formation of A–A in our irradiated system is obviously due to the well-known photodimerization of anthracene.

The photochemical dehydrogenation of HAH by MS–SM may now be represented as follows:

$$\text{MS–SM} \xrightarrow{h\nu} 2\text{MS}\cdot \qquad k_1 \qquad (5)$$

$$2\text{MS}\cdot \longrightarrow \text{MS–SM} \qquad k_2 \qquad (6)$$

$$\text{MS}\cdot + \text{HAH} \longrightarrow \text{MS–H} + \cdot\text{AH} \qquad k_3 \qquad (8)$$

$$2\cdot\text{AH} \longrightarrow \text{HA–AH} \qquad k_4 \qquad (9)$$

$$\text{MS}\cdot + \text{HA–AH} \longrightarrow \text{MS–H} + \text{A} + \cdot\text{AH} \qquad k_5 \qquad (10)$$

$$2\text{A} \xrightarrow{h\nu} \text{A–A} \qquad (11)$$

By employing a large excess of HAH, e.g. a molar ratio of HAH to MSSM of 20 : 1, thiol formation was found to be first-order with respect to disulphide. In this case (8) competes effectively with (6): virtually all MS· radicals formed are captured by the hydrogen donor and hence equation (12) obtains:

$$\frac{\text{d[MS}\cdot]}{\text{dt}} = 2k_1[\text{MS–SM}] - k_3[\text{MS}\cdot][\text{HAH}] = 0 \qquad (12)$$

$$\frac{\text{d[MSH]}}{\text{dt}} = k_3[\text{MS}\cdot][\text{HAH}] = 2k_1[\text{MS–SM}] \qquad (13)$$

$$k_1 t = -\ln(1 - x) \qquad (14)$$

where x denotes the fraction of MS–SM converted to MSH. This photochemical hydrogen-abstraction reaction only proceeds if the wavelength of the light used is

[6] P. Bruin, A. F. Bickel and E. C. Kooyman, *Rec. Trav. Chim.* **71**, 1115 (1952).
[7] J. L. Franklin and H. E. Lumpkin, *J. Amer. Chem. Soc.* **74**, 1023 (1952); S. Sunner, *Acta Chem. Scand.* **9**, 837 (1955).

shorter than 5000 Å, i.e. the energy of the light should exceed 57 kcal/mole of photons. In view of the strength of the S–S bond in disulphides which is estimated to be smaller than about 70 kcal/mole,[4,7] this seems to be a plausible wavelength limit.

(c) *Photo-dissociation of* MS–SM *in various solvents*

According to (14) the rate constant k_1 of photo-dissociation of MSSM can be obtained from measurements of thiol formation as a function of time in solutions of MSSM and a large excess of hydrogen donor, e.g. HAH. Of course, k_1 depends on the intensity of irradiation I and should properly be written $k_1 = k_1'.I$. Since all measurements were performed under standardized irradiation conditions, k_1-values may be used to describe the relative rates of the dissociation reaction. Quite pronounced differences were found upon varying the solvent, though in each case thiol formation

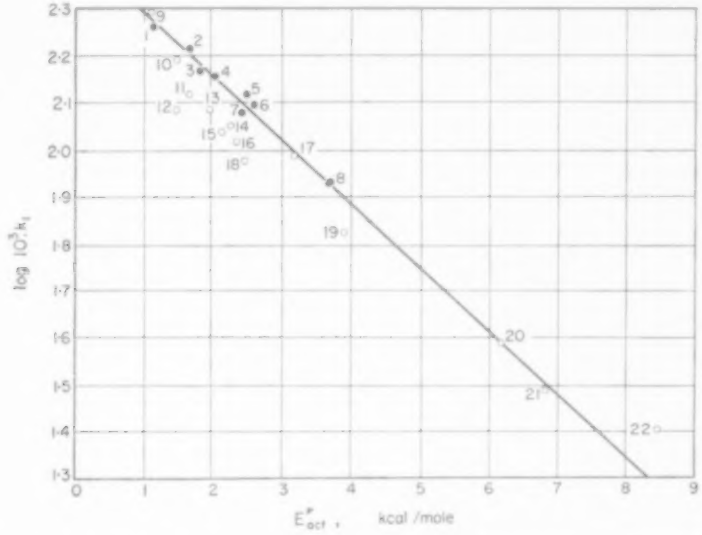

FIG. 1. Logarithm of the rate constant k, of photochemical dissociation of dimesityl disulphide vs. activation energy of kinematic viscous flow of the solvent; 25°C. 1—pentane; 2—heptane; 3—2,2,4-trimethyl pentane; 4—toluene; 5—decane; 6—toluene/hexadecane (37·5%v/62·5%v); 7—heptane/hexadecane (50%v/50%v); 8—hexadecane; 9—carbon disulphide; 10—acetone; 11—methyl acetate; 12—chloroform; 13—chlorobenzene; 14—equal parts by volume of heptane, toluene, hexadecane, chloroform, chlorobenzene, bromobenzene, carbon tetrachloride, cyclohexanone; 15—bromobenzene; 16—carbon tetrachloride; 17—cyclohexanone; 18—chlorobenzene + 5%w of polystyrene; 19—ethyl-*p*-ethylbenzoate; 20—hexadecane/dioctyl phthalate (37·5%v/62·5%v); 21—dimethyl phthalate; 22—dioctyl phthalate.

was first-order with respect to disulphide. Comparison of many pure solvents and solvent mixtures revealed that no direct relationships exist between the rates of dissociation and such solvent properties as dipole moment, polarizability or dielectric constant. Generally, rate constants k_1, were found to decrease with increasing kinematic viscosity of the solvent. Such a relationship seems plausible as the dissociation of a molecule is only complete when both fragments diffuse apart into the solution. Presumably, the dissociating molecule has to cope with the van der Waals forces in the solvent and actually, a fair correlation was found to exist between reaction

rates k_1 and the activation energy of kinematic viscous flow, calculated from the Arrhenius type equation for the temperature dependence of viscosity: $\log \nu = \log \nu_0 + E^{\nu}_{act}/2{\cdot}3\,RT$, as is illustrated by Fig. 1.

TABLE 3. RELATION BETWEEN VISCOSITY AND EQUILIBRIUM CONSTANT OF HEXAPHENYLETHANE DISSOCIATION

Solvent	Equilibrium constant at 20° log (K.10⁴)	Act. energy of kin. viscous flow E_{act}, kcal/mole
Carbon disulphide	1·28	1·08
Chloroform	0·84	1·43
Benzene	0·61	2·30
1,2-Dibromoethane	0·59	2·63
Bromobenzene	0·57	2·10
1,4-Dioxane	0·40	2·85
Acetophenone	0·23	3·09
Ethylbenzoate	0·22	3·54
Propionitrile	0·08	1·55

The same relationship was found to hold for the equilibrium constants of the thermal dissociation of hexaphenylethane, measured by Ziegler,[8] propionitrile being a notable exception, as is shown in Table 3.

[8] K. Ziegler and L. Ewald, *Liebigs Ann.* **473**, 163 (1929).

Tetrahedron, 1960, Vol. 10, pp. 81 to 95. Pergamon Press Ltd. Printed in Northern Ireland

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AN APPLICATION OF THE SEMI-EMPIRICAL MO–LCAO METHOD TO INDOXAZENE AND ANTHRANIL

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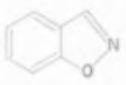
(*Received* 20 *October* 1959)

Abstract—A discussion, in the light of a simple MO-LCAO treatment with inclusion of overlap, of the structure and properties of the two benzisoxazoles, indoxazene and anthranil, is given. After a few comments about the method used, the results of calculations by use of Orgel's parameters are given. The practically equal values of the dipole moments of the two molecules are substantially reproduced and explained. The main points about the structure and reactivity of indoxazene and anthranil are re-examined, pending further experimental investigation.

I. INTRODUCTION

THE two possible benzisoxazoles, indoxazene (I) and anthranil (II), are both known. While indoxazene behaves substantially as any 4,5-disubstituted isoxazole, anthranil is very reactive, unlike the other 3,4-disubstituted isoxazoles. Its sensitivity to



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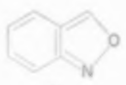

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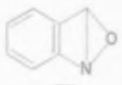

IV

carbonyl reagents led its discoverers[1] to propose for it a lactam structure III, which, after a long and bitter dispute,[2] was finally disproved, together with structure IV by means of optical investigations.[3] The establishment of a benzisoxazole structure makes the properties of anthranil an indication of a peculiar electron distribution. This is also indicated by the fact that the dipole moments of I and II are practically equal,[4] notwithstanding the difference in the σ-skeletons and the quinoid structure which the classical formula for anthranil is bound to contain.

The preceding remarks induced us to carry out a semi-empirical investigation about the compounds I and II, with the purpose of finding an electronic picture of these molecules and of deducing possible interpretations of their properties.

II. METHOD

The Hückel approach to molecular π-electron states has been used.

It is not intended here to give a detailed discussion of the validity and limitations of this method; however, a few comments about its present position, especially with respect to heterocyclic compounds, are appropriate.

Although an alternative procedure has been given,[5] the separation between σ and

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[1] P. Friedländer and R. Henriques, *Ber. Dtsch. Chem. Ges.* **15**, 2105 (1882); **28**, 1382 (1895).
[2] The main arguments in this dispute are summarized by E. Bamberger, *Ber. Dtsch. Chem. Ges.* **36**, 819 (1903).
[3] K. Von Auwers, *Liebigs Ann.* **437**, 63 (1924).
[4] K. A. Jensen and M. Friediger, *Kgl. Danske Videskab. Selzk* XX, No. 20 (1943).
[5] G. G. Hall, *Proc. Roy. Soc.* A **213**, 102, 113 (1952).

π states has been proved to be a reliable approximation.[6] The general connection between the Hückel approach and more strictly mathematical approximation to the properties of ground states of molecules has been discussed, both in the light of the Hartree–Fock scheme and its SCF–MO–LCAO form[7] and in the light of approximations including configuration interaction:[8] in the latter case, it has been concluded that the Hückel approach, with appropriate parameters, can give a good description of the ground states of molecules.

The investigations mentioned, and others of a similar type, however, have not attacked the problem of giving a sounder foundation to the physical picture which underlies the MO–LCAO method. Consequently, they are not especially illuminating as to the significance of such quantities as charge- and bond-orders, which, nevertheless, are extremely useful in chemical applications. In this connection it can be said that the only proof of the validity of the MO–LCAO picture of molecules lies in the usefulness in interpreting the properties of molecules. A short review of the present position in this respect has been given:[9] it supports fully the view that, in comparing similar molecules, the Hückel method can be very illuminating. The papers mentioned above show that, if used cautiously, it can give much better quantitative agreement with experiment than usually expected.

Mainly in connection with the latter point, one particular topic is of interest here, namely the so-called "non-orthogonality problem." While Dewar[9] seems to think that introduction of overlap is probably pointless, others[10] have pointed out that possibly much better quantitative results as well as the elimination of some serious inconsistencies would result from the inclusion of overlap in Hückel calculations. The theoretical problem of such an inclusion, and of correlating the results with those of an equivalent overlap neglecting calculation, has long since been solved;[11] also, it can be shown that, under certain very plausible assumptions, the inclusion of overlap does not affect the calculation of dipole moments and the definition of atomic charges, while the eigenvalues are modified according to a simple linear transformation,[12] as we shall briefly summarize in the next section.

III. INCLUSION OF OVERLAP

If one assumes that the overlap integrals, $\beta_{\mu\nu}$, are proportional to the corresponding bond integrals, $S_{\mu\nu}$, through a general constant λ,[7] the basic equation of the MO–LCAO method

$$\mathbf{HC} = (\mathbf{I} + \mathbf{S})\mathbf{C}\boldsymbol{\epsilon} \tag{1}$$

can be shown to be equivalent to an equation of the form

$$\mathbf{H}'\mathbf{C}' = \mathbf{C}'\boldsymbol{\epsilon}' \tag{2}$$

[6] P. G. Lykos and R. G. Parr, *J. Chem. Phys.* **24**, 1166 (1956).
[7] R. S. Mulliken, *J. Chem. Phys.* **46**, 497, 675 (1949).
[8] R. McWeeny, *Proc. Roy. Soc.* A **232**, 114 (1955); R. McWeeny and T. E. Peacock, *Proc. Phys. Soc.* **70**, 41 (1957).
[9] M. J. S. Dewar, *Ann. Rep. Chem. Soc.* **53**, 126 (1956). About charges and bond-orders see also N. S. Ham and K. Ruebenderg, *J. Chem. Phys.* **29**, 1195, 1215, 1229, 1232 (1958).
[10] P. O. Löwdin, *J. Chem. Phys.* **21**, 496 (1953) and references therein.
[11] P. O. Löwdin, *Arkiv. Mat. Astr. Fys.* **35A**, 9 (1947); *A Theoretical Investigation into some Properties of Ionic Crystals* (Thesis) Almqvist and Wiksell, Uppsala, Sweden (1948); *J. Chem. Phys.* **18**, 365, (1950).
[12] G. Del Re, *On the Non-orthogonality Problem in the Semi-empirical MO–LCAO Method.* Quantum Chemistry Group of Uppsala University, Uppsala, Sweden, Techn. Rep. No. 20 (1958).

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if the connexion between quantities in (2) and (1) is [primed quantities refer to (2)]:

$$\epsilon_i = \frac{\epsilon_i'}{1 + \lambda\epsilon_i'}\,; \tag{3}$$

$$\alpha_\mu = \frac{\alpha_\mu'}{1 + \lambda\alpha_\mu'}\,; \qquad \beta_{\mu\nu} = \frac{\beta_{\mu\nu}'}{\sqrt{(1 + \lambda\alpha_\mu')(1 + \lambda\alpha_\nu')}} \tag{4}$$

$$C_{\mu i} = \sqrt{\frac{1 + \lambda\alpha_\mu'}{1 + \lambda\epsilon_i'}}\, C_{\mu i}'. \tag{5}$$

In these equations the symbols have the usual meanings of orbital energies (ϵ_i), coulomb integrals (α_μ), bond-integrals ($\beta_{\mu\nu}$) and coefficients of the expansion of the i-th molecular orbital in the atomic orbitals ϕ_μ ($\epsilon_{\mu i}$). Their importance is connected with the fact that, since the diagonal and off-diagonal elements α_μ' and $\beta_{\mu\nu}'$ of $\mathbf{H}'$ have the same one-atom and one-bond dependence as the corresponding elements of $\mathbf{H}$, they can be taken as empirical parameters—provided a physical meaning is given only to quantities appearing in equation (2).

Now, it can also be shown that, provided the atomic orbitals are not very different in "size" and the overlap integrals are comparatively small (which is the case with π-electron systems) the dipole moments of π-electrons in a conjugated system can be described very well by atomic charges derived directly from (2), i.e. just as in calculations neglecting overlap. The preceding deductions can also be phrased as follows: *for applications where only energies and charges are required, one can start directly from an overlap-neglecting calculation, and overlap can then be taken into account through the linear transformation* (3) *of the eigenvalues.*

IV. PARAMETERS

As usual, we shall use α and β as standard reference parameters. For atoms μ and ν we shall therefore write:

$$\begin{aligned} \alpha_\mu &= \alpha + \delta_\mu\beta, \\ \alpha_\nu &= \alpha + \delta_\nu\beta, \\ \beta_{\mu\nu} &= \eta_{\mu\nu}\beta. \end{aligned} \tag{6}$$

As to the values of the quantities δ and η, their choice is subject, as is well known, to a large degree of arbitrariness: this, however, does not influence very much the semi-quantitative significance of the results, so that, provided certain general requirements are fulfilled, the particular choice of the parameters is not too important. Anyway, since we are interested both in considering dipole moments and in getting as good charges as possible, we shall use the set of parameters given in Table 1, which has been suggested just to predict the dipole moments of heterocyclic molecules, for instance isoxazole[13].

Two objections to the choice of this set deserve some comments. First, the introduction of 'inductive effects' into δ_C has been criticized as being theoretically unsound.[8] Such a criticism seemed also supported by the remark that a Hückel Hamiltonian corresponding to a more rigorous one does not show any increase in

[13] L. E. Orgel, T. L. Cottrell, W. Dick and L. E. Sutton, *Trans. Faraday Soc.* **47**, 113 (1951).

parameters for carbon atoms surrounding a heteroatom. However, it turns out (for instance in the case of furan and anisole) that it is practically impossible to find a set of parameters which predict a correct charge distribution for different molecules if no 'inductive effect' is taken into account. A similar remark has been made by others.[14] Therefore, the argument in the original paper[15] where the use of 'inductive' corrections was suggested appears to be rather well based from the empirical point of view. One could also introduce a sort of intuitive argument to justify this procedure. In the

TABLE 1. PARAMETERS USED IN THESE CALCULATIONS

$\delta_C = 0{\cdot}1\Sigma\delta_x^a$	$\eta_{CC} = 1{\cdot}0$
$\delta_{X<} = 1{\cdot}0$	$\eta_{CX} = 1{\cdot}2$
$\delta_{S<} = 2{\cdot}0$	$\eta_{CO} = 1{\cdot}4$
$\delta_{O=} = 2{\cdot}0$	$\eta_{SO} = 0{\cdot}6$
$\delta_{O<} = 3{\cdot}2$	$\lambda = 0{\cdot}25$

ax denotes heteroatoms adjacent to C.

Hückel method, as is well known, the integrals $\alpha_\mu = \int \phi_\mu^* \mathscr{H}_{eff} \phi_\mu \, d\tau$ are taken as not depending upon the actual molecule one is considering in each case. If a physical meaning is to be given to this assumption, this is that the field generated at the center μ by neighbouring atoms (which only matters in a nearest neighbour approximation is practically independent of their nature; a statement which would be true enough if it were taken to mean that neighbours are "seen" from an atom μ as if, so to say, the same effective charge always correspond to their cores. Now, even if such a drastic simplification were justified in general, it certainly would not if one of more of the neighbours of μ happened to exhibit abnormal covalency, as for instance nitrogen in pyrrole, since then the cores would be quite different. The introduction of a correction in δ_μ is therefore necessary, at least in these cases, especially if δ_μ is so low that a slight change in it can affect strongly the charge distribution. It is easy to see how the preceding argument can be used to justify the actual way this "inductive effect" is introduced; however, it should be remembered that intuitive arguments as the one above cannot be taken too literally, and the best justification for the form given to the 'inductive effect' is that it works.

The second objection to the parameters chosen arises from the fact that the dipole moments obtained by Orgel *et al.* for the π-systems of heteromolecules are larger by a factor 1·6 than the experimental value; as a matter of fact, a correction in the parameters would be welcome. However, the proportionality between the calculated and experimental moments stands in favour of the correctness of the "relative" distributions of charges: and, for our purpose, the absolute magnitudes of the latter are not important. As to the energies, they too are obviously dependent upon the choice of parameters: but, even for these, we can consider their relative values, if a comparison between similar molecules is our only purpose.

[14] B. Pullman and A. Pullman, *Proc. Nat. Acad. Sci.* **45**, 136 (1959).
[15] L. Pauling and G. W. Wheland, *J. Amer. Chem. Soc.* **57**, 2086 (1935).

The last parameter we must consider is λ (see section II): to it we have attributed a value of 0·25 because this value has usually been attributed to the overlap integral of the CC π-bond.

V. RESULTS AND DISCUSSION

The diagrams of Fig. 1 and Fig. 2 show the results for charge- and bond-orders for isoxazole (as calculated by Orgel *et al.*[13]) and for the two molecules under study here. Tables 2, 3 and 4 show some results about energies and dipole moments.

We shall first of all discuss energies, then the structures of the molecules under study in the light of results about dipole moments, charge- and bond-orders. In another section we shall use these results to discuss reactivities.

A. Total and delocalization energies

The main use one can make of energies calculated for ground states of molecules by means of the semi-empirical MO–LCAO method is for comparisons between different molecules. We have therefore included additional data to make such comparisons easier in Tables 2 and 3. Table 2 contains (a) total calculated energies, (b) delocalization energies, (c) delocalization energies per electron.

According to a remark by Orgel *et al.*,[13] we have avoided introducing resonance energies, but have used instead delocalization energies, simply calculated as the differences between total energies and the energies obtained by assigning the electrons to the various atomic orbitals with energies α_μ [see equation (4)]. In calculating the latter energies we have made no allowance for the "inductive effect," since we consider it as an effect of the binding.

The introduction of delocalization energies per electron deserves some comments. We have calculated them by dividing the whole delocalization energy by the number of electrons, with the purpose of comparing stabilities with a different number of π-electrons. These quantities, of course, are not strictly related to experimental quantities, since they are averages: nevertheless in our opinion they can be taken as a measure of the degree of delocalization of a system, since they are independent of the number of electrons.

From Table 2 it is immediately seen that the degree of delocalization of isoxazole is rather poor: this is not surprising, since the aromaticity of five-membered heterocyclics is always small, as is experimentally well known.[16] In fact, the total delocalization energy of isoxazole is only slightly larger than that of butadiene. As to the two molecules under study here, Table 2 shows that their aromatic nature is enormously increased with respect to isoxazole, because of the butadiene bridge linking two adjacent carbon atoms of the isoxazole unit. The fact that anthranil appears to be less stabilized than indoxazene clearly corresponds to the prevailing quinoid structure of the former compound. However, it is remarkable that the difference in delocalization energy per electron between the two benzisoxazoles is quite small, compared with the variation of this quantity when two isolated double bonds are allowed to interact (cf. ethylene and butadiene): this is an indication of the high weight of "ionic" structures in anthranil, as can be seen also from charge distributions. Table 2 also indicates that the increase in delocalization energy per electron from cyclopentadienyl to benzocyclopentadienyl is much less than the corresponding increase from isoxazole

[16] L. Fieser and M. Fieser, *Organic Chemistry*. Reinhold, New York (1956).

to any of the two benzisoxazoles. This is but one more example of the well known stabilizing effect of condensed benzene rings on heterocyclics.

B. Partial localization energies

Though other conclusions can be drawn from Table 2, the figures given there do not allow a complete analysis of the numerical data, because they give no insight into the relationships between the energies of molecules and those of their "building blocks," on whose properties most of the purely chemical theory of reactions bases

TABLE 2. TOTAL AND DELOCALIZATION ENERGIES

Compound	(a)	(b)	(c)
Ethylene	$2\alpha + 1{\cdot}600\beta$	1·600	0·800
Allyl neg. ion	$4\alpha + 2{\cdot}090\beta$	2·090	0·522
Oxime group	$4\alpha + 6{\cdot}030\beta$	1·674	0·418
CON-group	$4\alpha + 5{\cdot}452\beta$	1·090	0·273
Butadiene	$4\alpha + 3{\cdot}375\beta$	3·375	0·844
Cyclopentadienyl* neg. ion	$6\alpha + 4{\cdot}808\beta$	4·808	0·801
Isoxazole†	$6\alpha + 8{\cdot}116\beta$	3·760	0·627
Benzene*	$6\alpha + 5{\cdot}867\beta$	5·867	0·978
Pyridine*	$6\alpha + 6{\cdot}786\beta$	5·986	0·998
Benzocyclopentadienyl ion*	$10\alpha + 8{\cdot}789\beta$	8·789	0·879
Indoxazene	$10\alpha + 12{\cdot}237\beta$	7·881	0·788
Anthranil	$10\alpha + 12{\cdot}039\beta$	7·683	0·768

* From: B. Pullman and A. Y. Pullman, *Les Théories Electroniques de la Chimie Organique*. Masson, Paris (1952).
† Ref. 13.

(a) Total energies (overlap included).
(b) Delocalization energies in units β.
(c) Delocalization energies per electron, units β.

its predictions. In this connexion, a further elaboration of the results about energies is needed, and can be introduced by defining a *partial localization energy* as follows. Let the molecule under study be formed of two units, X and Y, linked to each other by any number of bonds (and, since we are considering π-systems, also conjugated to each other through these bonds). We shall call partial localization energy of the X unit in XY the difference between the total delocalization energy of XY and the delocalization energy calculated for Y. It corresponds to the energy needed to suppress the π-system of the X unit, by localizing its π-electrons, and gives an indication of the relative stability of X in a series of homologous molecules XY_1, XY_2, XY_3, etc.

The significance of such a quantity is clear if one considers the importance a reaction involving a whole unit can have for chemists—for instance, the oxidation of a polynuclear hydrocarbon. A quantity similar to these partial localization energies has been introduced by Brown[17] with respect to one bond, and hence called "bond fixation energy."

[17] R. D. Brown, *J. Chem. Soc.* 1951 (1955).

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As to the figures given in Table 3, the following remarks are important in connection with the present purpose:

(a) The 3,4-bond of isoxazole is more stable than the 4,5-bond, and indeed almost as stable as a CC-bond in a cyclopentadienyl system. This is not surprising, since it corresponds to the fact that localizing the two π-electrons of the 3,4-bond implies leaving a system whose only possibility of delocalization depends upon the tendency of oxygen to share its $2p\pi$ lone pair, which is obviously not very strong. On

TABLE 3. PARTIAL LOCALIZATION ENERGIES (units β)

Compound	Fixated part	Energy required
Butadiene	C=C bond	1·875
Cyclopentadienyl ion	C=C bond	2·718
	CCC unit	3·208
Isoxazole	3,4 bond	2·670
	4,5 bond	2·080
CNO unit	CNO unit	2·160
	CON unit	2·160
Benzene	C=C bond	2·492
	butadiene unit	4·267
Benzocyclopentadienyl ion	CCC unit	2·922
	butadiene unit	3·981
	cyclopentad. ring	5·414
	benzene ring	6·699
Indoxazene	CNO unit	2·014
	butadiene unit	4·121
	isoxazole ring	4·505
	benzene ring	6·207
Anthranil	CON unit	1·816
	butadiene unit	3·923
	isoxazole ring	4·308
	benzene ring	6·593

the other hand, fixing the 4,5-bond would leave the molecule with an oxime system, which is comparatively stable.

(b) In benzocyclopentadienyl the benzene ring appears to be very stable, even more stable than benzene itself. The large amount of 'extra resonance energy' with respect to any two component units explains the fact that all units appear to be very stable. However, the cyclopentadienyl unit is less stabilized than the benzene unit, with respect to the isolated molecule. This situation is entirely reversed in indoxazene. In fact, while the benzene unit still appears to be deactivated, the isoxazole unit is much more stabilized with respect to isoxazole itself, and this is in agreement with experiment (*vide infra*): the isoxazole unit of indoxazene is comparatively stable.

(c) As to anthranil, it shows two interesting facts: first, the isoxazole unit is much less stabilized than the benzene unit; second, the latter appears to be more stabilized than in indoxazene. This is already a first indication of the peculiar reactivity of anthranil; we shall return later to this point. In the same connection,

we note that the CON unit of anthranil shows an enormous increment of stability, with respect to its 'isolated' state, although it remains less stable than in isoxazole. This shows that its properties should be profoundly modified, with respect to its isolated, extremely unstable state, but that it should also be less stable than in isoxazole. In other words, anthranil should undergo more easily than isoxazole reactions which involve cleavage of one bond of the CON unit.

C. Dipole moments

As we pointed out in the introduction to the present paper, it is very surprising,

TABLE 4. DIPOLE MOMENTS (D)

Compound	μ_σ[a]	θ_σ[b]	μ_π[c]	θ_π[b]	μ^d_{tot}	μ^e_{obs}
Isoxazole[f]	1·9	155°	1·3	85°	2·7	2·8
Indoxazene	2·0	157°	1·3	119°	3·1	3·0
Anthranil	2·0	154°	2·6	82°	3·6	3·1

a Dipole moment of the σ-frame according to reference 13.
b Angles measured with respect to the vertical axis (Fig. 1); the signs of the moments are taken according to the chemical convention.
c Dipole moments of the π-charge distribution.
d Total calculated moment
e Total observed moment (Ref. 4).
f All values from Ref. 13.

at first sight, that the dipole moments of the two benzisoxazoles should be practically equal.[4] Indoxazene, judging from its chemical formula, is very similar to isoxazole, so that one should actually expect its dipole moment to be approximately the same as those of 4- and 5-phenylisoxazole, which are 3·0 and 3·2 D respectively.[18]

Anthranil, on the other hand, has a quinoid structure as a basic formula, so that it should be expected that highly polarized structures are essential for the stabilization of the whole system (*vide infra*). Therefore the result of the calculation of both dipole moments by means of the Hückel approach is particularly interesting, and Table 4 shows that the apparent equality of the dipole moments of the two benzisoxazoles is more or less an accident, due to the different orientation of the σ-moments in the two compounds, with respect to the corresponding π-moments. In fact, the π-dipole moment of anthranil is actually much larger than that of both isoxazole and indoxazene.

D. Charge distributions

It is instructive to discuss the dipole moments of the three compounds under study in connection with the charge distributions given in Fig. 1. An inspection of the charges in isoxazole suggests that two effects are superimposed in the π-system of this compound: one is the normal tendency of the charges to alternate, the other is the tendency of the electrons to concentrate on the nitrogen atom in such a way that the charge distribution tends to be symmetrical around the axis passing through the nitrogen atom. That the resulting charge distribution is not an accidental result of

[18] P. Pino and G. Speroni, *Rend. Ist. Lomb. Sci. Lett., Classe Sci.* **88**, 331 (1955).

the rough approximation used to derive it is shown by the fact that the direction of the dipole moment found for isoxazole agrees very well with experimental results.[19] Therefore, we can reasonably believe that also for the other two compounds the situation is correctly described by the charge distribution given in Fig. 1. In indoxazene, the tendency of the charge to be symmetrical around the longitudinal axis passing through nitrogen is even more marked than in isoxazole, as is shown by the direction

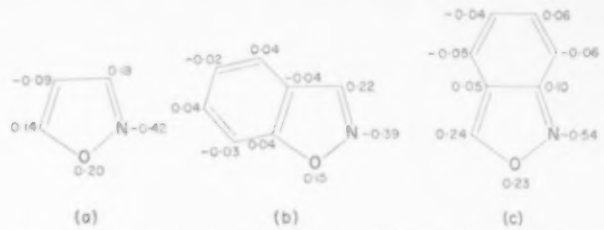

FIG. 1. Charge distributions found for (a) isoxazole[13], (b) indoxazene, (c) anthranil.

of the π-dipole moment. This is also true for bond orders, which, except for the CNO unit, are essentially symmetrical. In anthranil a quite different combination of the two effects is found. While the bond orders are symmetrical around the main longitudinal axis, thus supporting the fundamental quinoid structure of this benzisoxazole, the charge is very much concentrated on the nitrogen atom. This also corresponds to the fact that decreasing the bond order of the CN bond increases the charge of nitrogen; this may be considered as the Hückel equivalent of the introduction of ionic structures which would be required if resonance theory were applied to explain the 'aromaticity' of anthranil.

It is also useful to correlate the partial localization energies given in Table 3 with the molecular diagrams of Fig. 1. The isoxazole unit is stabilized by the condensed benzene ring both in indoxazene and in anthranil, but more in the former compound than in the latter. The stabilizing effect of the benzene ring, as we have pointed out before, is a well-known effect: here we only note that, at first sight, it seems to have very little to do with the charge distribution. In fact, there is no apparent general increase in bond-orders and no levelling of charges in passing from isoxazole to its two benzo-derivatives. However, if one considers the overall charge on the isoxazole ring, one understands where the correlation lies. In fact, the charge on the isoxazole ring, which is zero by definition in isoxazole, is —0·021 in indoxazene and —0·016 in anthranil, so that it clearly corresponds to the sequence indoxazene–anthranil–isoxazole suggested by partial localization energies. It is certainly remarkable that differences in localization energies of 0·554 and 0·752 should correspond to an excess of negative charge so small that we have been obliged to use three decimal figures to make the difference evident. However, this is no surprise if one considers that, especially in five-membered rings, this high sensitivity of energies to charges is the rule.

E. Bond orders

As to bond orders, there appears to be no easy way of connecting them with localization energies, also because, as we have pointed out in section III, they have no direct meaning if overlap is considered as important, except in a very rough way.

[19] G. Speroni and P. Pino, *Gazz. Chim. Ital.* **80**, 549 (1950); **82**, 269, 285 (1952); **84**, 760 (1954).

However, their qualitative distribution shows how close the structures of indoxazene and anthranil are to the classical structures one can draw for these compounds. In indoxazene, the benzene ring appears to be mainly in its normal kekule structures, except for an important contribution on the part of a quinoid structure which is apparently the consequence of the conjugation through oxygen to the isoxazole system. It is remarkable that there appears to be a very well localized CN bond, more

(a) (b) (c)

FIG. 2. Bond-orders of (a) isoxazole,[18] (b) indoxazene, (c) anthranil.

localized, indeed, than the corresponding one in isoxazole. This may very well correspond to the fact that the mesomeric effect of oxygen influences the benzene ring mainly through the CN bond, instead than directly, so that the conjugated system is substantially that of benzaldoxime, whose U.V. spectrum is indeed very similar to that of indoxazene.[20] This conclusion is supported by the remark that the effect of oxygen when conjugated to a phenyl group through a NC bond is to increase the bond order of the CN bond: this was shown in a study of benzonitriloxide as compared to benzonitrile[21] by simple Hückel calculations and supported by the experimental results of an infra-red study of the same compounds.[22]

In anthranil, as we have said, the quinoid structure appears to be favoured in our molecular diagram. Substantially, a comparison with isoxazole shows that two effects are superimposed in this compound: (a) the typical delocalization of an isolated benzene ring, (b) the delocalization along the perimeter of the molecule, leading to an increase of the NO and CO bond orders, and a decrease of the CN bond order. The latter effect corresponds to the fact that no aromaticity and practically no stability as a ring compound could be expected for anthranil if the quinoid structure were not accompanied by a closure of the conjugation through the oxygen atom. This also means that, since there appears to be such a conjugation, the present treatment agrees perfectly with the now established structure II for the anthranil molecule. It is also interesting to remember here that in anthranil the partial localization energy of the benzene ring is much higher than in indoxazene. This is apparently due to the great amount of conjugation which is needed to stabilize the CON unit. For the same reason a smaller partial delocalization energy corresponds to the isoxazole unit of anthranil, as compared to that of indoxazene.

VI. REACTIONS OF INDOXAZENE AND ANTHRANIL

Even if many objections can be made to the use of charges, as calculated by the naïve Hückel method, in discussing reactivities,[23] the intuitive electrostatic model of

[20] P. Grammaticakis, *Bull. Soc. Chim. Fr.* **V8**, 101 (1941).
[21] G. Del Re, *Atti Accad. Lincei* **22**, 491 (1957).
[22] S. Califano, R. Moccia, R. Scarpati and G. Speroni, *J. Chem. Phys.* **26**, 1777(L) (1957).
[23] R. D. Brown, *Quart. Rev.* **6**, 62 (1952).

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reactions appears to be rather consistent with experimental facts (as far as ionic reactions are concerned), when they are used only to predict the direction of a certain reaction will take where large differences in atomic charges are found, as it happens in compounds containing heteroatoms. Therefore, with some reservations, we shall use them to discuss a few reactions of the two compounds under study.

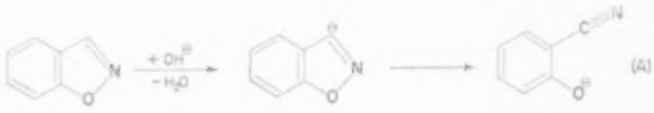
The preceding discussion of charge- and bond-orders has shown a few general points. In both compounds the reactivity is practically localized in the isoxazole ring, the CNO unit of indoxazene being just a little less stable than that of isoxazole, while the CON unit of anthranil is markedly less stable than that of isoxazole. Therefore, the comparatively high reactivity of both compounds and the particular sensitivity to many reagents of the part of anthranil are indicated by our previous results. As to the benzene units, if an electrophilic substitution can be carried out without destroying the isoxazole ring, our molecular diagrams predict that substituents will enter *ortho-para* to the CO bond in indoxazene, *ortho-para* to the CN bond in anthranil: the substitution itself should be comparatively more selective in anthranil than in indoxazene, according to charges—though, as far as Table 3 goes, indoxazene should undergo substitutions somewhat more easily, since its benzene unit is less deactivated than that of anthranil.

The fact that the benzene rings of both compounds act as an electron donor (section VD) suggests that an electron attracting group on the benzene ring should cause a destabilization of both compounds. One instance at least is known:[24] 6-nitro-indoxazene cannot be isolated when obtained from the appropriate oxime, because it undergoes immediately transformation to a salicylo derivative (see following subsection).

Apart from the above general remarks, we will now consider a few examples of reactions of the compound under study in more detail.

A. Indoxazene

The reactions of indoxazene are those typical of an isoxazole derivative, in agreement with all our preceding results. The most interesting one is the formation, with alkali, of a nitrile derivative. The following mechanism has been proposed for this



I V VI

reaction[25] in the case of isoxazole. Such a mechanism implies the loss of a hydrogen atom by indoxazene, followed by a cleavage of the N–O bond. There is some support for this mechanism from the semi-theoretical point of view. The high positive charge of the carbon atom adjacent to nitrogen can serve as a justification for the easy cleavage of the C_3-H bond, and, while ion V in itself cannot be expected to be more stable than I, it certainly has a smaller proton affinity than the OH^- ion, thus making the reaction I → V very plausible.

[24] J. Meisenheimer, P. Zimmermann and U. V. Kummer, *Liebigs Ann.* **446**, 205 (1926).
[25] G. Speroni and P. Pino, *Atti Accad. Lincei* **VIII**, 6, 325 (1949).

One can also predict that, given the higher positive charge of carbon 3 in indoxazene with respect to isoxazole, the stage in question should occur more easily in the former compound, i.e., for instance, at a lower pH.

The second stage of the reaction (A) involves only a rearrangement of the ion V, and therefore should be a rather fast step, with little, if any, activation energy involved. Although this stage is entirely justified by chemical experience, because ion VI is known to be a very stable one, whereas ions of a type like V are in general only short-lived intermediates, it is interesting to examine this point in the light of semi-empirical calculations. If the effect of negative charges on coulomb integrals is neglected, the energies of the π-systems of V and VI are $10\alpha + 12{\cdot}237\beta$ and $10\alpha + 12{\cdot}180\beta$ respectively, so that the difference is in favour of ion V for $0{\cdot}057\beta$. If, just for the sake of a better interpretation of this figure, we give β a value of -33 kcal/mole[26] we have that the π-system of ion V should be more stable by about 2 kcal/mole than that of ion V. Even if one considers the fact that in ion VI the N–O bond of V is replaced by a π'-C–N bond, one finds that the energies of the two ions are practically the same, since the energies of the two bonds just mentioned are of the same order of magnitude.[27] Therefore, if one does not consider explicitly the negative charge, neither of the two ions is actually favoured. However, the negative charge actually plays an important role in this reaction, since in the salicylonitrile ion the repulsion between the phenate oxygen and the nitrile nitrogen, both highly negative, makes a ring closure improbable, while a similar reason should favour very much the opening of the ring in ion V.

As we have already pointed out, the reaction so far discussed, as well as the others indoxazene undergoes, is substantially similar to the corresponding reactions of the isoxazole with no substituents in position 3, as a comparison between the charges of isoxazole and indoxazene (Fig. 1) immediately shows.

B. Anthranil

The case of anthranil is much different. First of all, isoxazoles having substituents in their 3-positions usually show a high stability towards alkali,[28] which is not the case of anthranil[1] as has also been deduced from Table 3. This remark, together with the fact that the charge of carbon 5 of the isoxazole ring in the latter compound is even higher than the charge of carbon 3 in isoxazole and indoxazene, supports the suggestion, originally due to Schmidt,[29] that in anthranil the hydrogen belonging to the isoxazole unit is labile. One should therefore suggest a tautomerism—at least potential—of the type (B):

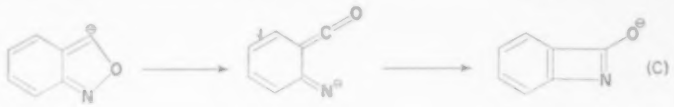
(B)

II VII

This kind of tautomerism implies the formation of an ion similar to ion V [see (A)] which, in strong alkaline media, might rearrange to another ion IX which should then

[26] G. W. Wheland, *Resonance in Organic Chemistry* p. 669. John Wiley, New York (1955).
[27] T. L. Cottrell, *The Strengths of Chemical Bonds*. Butterworths, London (1954).
[28] L. Claisen, *Ber. Dtsch. Chem. Ges.* **24**, 3904 (1891); more recent work on isoxazoles is to be found in the work of A. Quilico *et al.* mainly in *Gazz. Chim. Ital.*[19]
[29] O. Schmidt, *Ber. Dtsch. Chem. Ges.* **36**, 2459, (1903).

behave as a ketene derivative; this could even undergo a further rearrangement (C) leading to the formation of a four-membered ring of the lactam type. Such a rearrangement would just give the ion corresponding to the structure III proposed for anthranil for its discoverers.[1] The reason for suggesting the existence of X, as a short lived intermediate, is that ions with a negative charge localized on a nitrogen atom are not very likely. However, it must be noted that from an experimental point of view it is doubtful whether it would be possible to distinguish between IX and X,



VIII IX X

since both are to be considered as short lived intermediates: the question is only interesting in connection with the formulation of reaction mechanisms. From the semi-theoretical point of view, if, as usual, we neglect the effect of negative charges on coulomb integrals, the energies of the π-systems of VIII, IX and X are found to be respectively: $10\alpha + 12{\cdot}237\beta$, $10\alpha + 11{\cdot}938\beta$, $10\alpha + 12{\cdot}057\beta$. If we evaluate the total energy differences in (C) by use of bond energies[27] and of the preceding figures (β being taken again as -33 kcal/mole[26]), we find:

$$E\ (VIII \rightarrow IX): \quad -31 \text{ kcal/mole};$$

$$E\ (IX \rightarrow IX): \quad +25 \text{ kcal/mole};$$

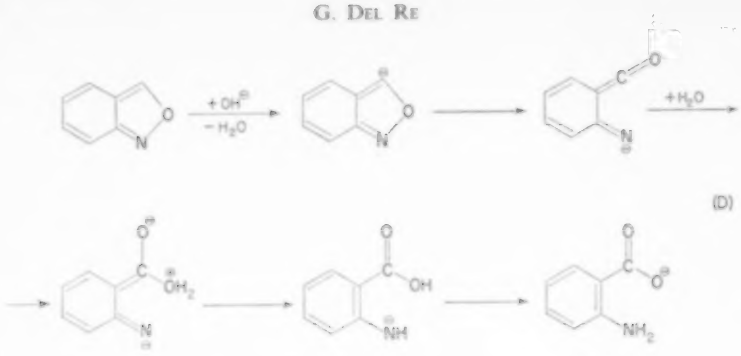
$$E\ (VIII \rightarrow X): \quad -6 \text{ kcal/mole}.$$

Therefore, all reservations made about the validity of these figures, we are led to assume that the most probable form of the ion in discussion here is the form IX. Here again, however, we must remark that it is extremely probable that ion X, once formed, is extremely more stable than IX for a reason our calculations have not taken into account, i.e. the possibility the negative charge of X has to spread over the whole molecule, which should make X much less reactive than IX. Curiously enough, even this consideration leads us to consider IX as the most appropriate intermediate for the reactions in alkaline media, since we can assume that the unimolecular step leading to the formation of a strained ring such as the lactam ring is slower than other reactions which IX should undergo more readily than X, especially those involving either the nitrogen atom or the ketene group. Therefore, the following scheme for the formation of anthranilic acid (XI) from indoxazene in strong alkaline media seems to be quite plausible.

Among the many other reactions of anthranil, we shall discuss here only one, which has been a very important point in the dispute about its structure.[2] This is the addition of hydroxylamine to anthranil, which obliged even those who supported the isoxazole formula to agree that "the aldehydic character, although not typical of anthranil as such, is to some extent latent" in it.[30]

From the point of view of the semi-theoretical treatment, what is really important in this connection is not whether anthranil contains a carbonyl group, but whether it

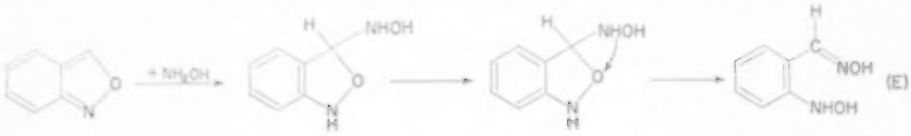
[30] E. Bamberger and E. Demuth, *Ber. Dtsch. Chem. Ges.* **34**, 4015 (1901).



(D)

XI

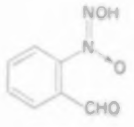
can undergo reactions typical of this group. It is not probable that, in the environment in which addition of hydroxylamine is usually carried out, any importance should be attributed to the formation of negative ions by anthranil. Therefore, the static diagram of Fig. 1 should be considered. Here again, the high positive charge of carbon 5 appears to give an explanation for this peculiar reaction. By analogy with the typical reactions of formation of oximes,[31] a mechanism can be formulated roughly as follows:



(E)

The only difference between mechanism (E) and that of the usual oxime forming reactions is the attack of a proton to nitrogen. This is justified by the fact that nitrogen, according to Fig. 1, is very negative in the ground state of anthranil and that steps (a) and (b) are probably simultaneous. Therefore, we can say that the 'latent aldehydic character' of anthranil is a result of both the high positive charge of its carbon atom and of the negative charge of nitrogen: the latter is probably essential in order that the attack of hydroxylamine may be followed by the actual formation of an oxime.

The high negative charge of nitrogen in anthranil suggests also that this compound should be basic. This is quite possible, since isoxazole itself is slightly basic:[25] however, there is no information, at least as far as we know, about this property of anthranil. The only reaction that can be correlated with the basic properties of anthranil is its ability to give a diazonium salt with $NaNO_2$ and strong sulphuric acid.[32] However, it is impossible here to give a mechanism for this reaction, since it proceeds through the formation of a nitrosophenylhydroxylamine derivative, XIII.



XIII

which corresponds to the product of a simultaneous nitrosation and oxidation

[31] H. Meerwein, O. Fuchs, H. J. Sasse, H. Schrodt and J. Spille, *Ber. Dtsch. Chem. Ges.* **89**, 2060 (1956); see also ref. 16.

[32] E. Bamberger and J. Lublin, *Ber. Dtsch. Chem. Ges.* **42**, 1723 (1909); see also A. A. Morton, *The Chemistry of Heterocyclic Compounds* p. 426. McGraw-Hill, New York (1946).

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VII. CONCLUSION

As we have already mentioned, the naïve Hückel method is not only open to very serious theoretical objections, but is far from having reached a well determined status as an interpolation procedure inspired by the formalism of quantum mechanics. Therefore, in a research like the one we have presented, two aspects are bound to be present: the particular application of the method as a scheme for correlating properties of certain compounds to each other and to those of other compounds, and a critical analysis of the "theoretical" quantities used to get such a correlation.

In our particular case, we have tried to reach our main purpose—that of interpreting in terms of a general scheme the properties of indoxazene and anthranil—by using only a limited amount of numerical data, in order to avoid the risk of introducing too many definitions.

The conclusions we have reached are as follows:

(a). The comparatively good stability of indoxazene and anthranil is predicted in our results and is to be attributed to the stabilizing effect of the benzene ring condensed to the isoxazole unit;

(b). The peculiar properties of anthranil, as compared to similar isoxazole derivatives, are correctly interpreted in the frame of the method used, under the assumption that anthranil is actually an isoxazole derivative;

(c). The reactivities of both benzisoxazoles appear to agree with the charges found for their π-electron systems.

These conclusions are mainly of a semi-qualitative nature, and this is not surprising, since it is probable that the semi-empirical MO–LCAO approach cannot give more than this sort of information. However, within such a limitation, it appears to work: and we can reasonably expect that many of its conclusions are reliable.

In our particular case, one is especially interesting, namely the existence and stability of the positive and negative ions derived from the two benzisoxazoles. A careful investigation of this problem from the experimental point of view would be very appropriate.

Also the effect of electron attracting or electron releasing substituents in various positions would be of great interest; in particular the variation of the dipole moments and of the reactivity of these two compounds after substitution might probably lead to very interesting advances in the chemistry of heterocyclics.

Acknowledgements—The Author wishes to thank Professor Giovanni Speroni, of the University of Florence, Italy, for having suggested this work and assisted the Author with his advice; and Professor Harrison Shull, Indiana University, Bloomington, U.S.A., for having read and discussed the manuscript with him. The author also wishes to thank the Quantum Chemistry Group of Uppsala University for the warm hospitality and the stimulating environment in which this work was completed.

Tetrahedron, 1960, Vol. 10, pp. 96 to 101. Pergamon Press Ltd. Printed in Northern Ireland

THE ABSORPTION SPECTRA OF MOLECULAR COMPLEXES

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(*Received* 30 *December* 1959)

Abstract—The intermolecular charge-transfer absorption spectra of complexes of various p-π aromatic electron donor molecules with a series of p-π aromatic electron acceptor molecules have been measured. The frequencies of the bands of these complexes may be expressed simply as the sum of two terms, characteristic of the donor and acceptor molecules respectively. This relationship fails if the electron donor is weak.

THE molecular complexes between electron donors and electron acceptors usually show new electronic absorption transitions not observed in either component alone. One group of such interactions involves heats of formation in the ground state of the order 1–5 kcal/mole. These have been described by Mulliken[1] as outer complexes, and his interpretation that the new bands are intermolecular charge-transfer transitions is now generally accepted.

Many regularities in the absorption spectra have been observed: in particular McConnell *et al.*[2] have demonstrated the approximate linearity between the maximum extinction coefficient of the charge-transfer band (ε) and the wavelength at which this occurs (λ) for complexes of the donor benzene with various acceptors. The acceptors,

TABLE 1. MOLAR EXTINCTION COEFFICIENTS (ε) AND WAVELENGTHS (λ) OF MAXIMUM ABSORPTION OF HEXAMETHYLBENZENE COMPLEXES IN CARBON TETRACHLORIDE

Acceptor	ε (l. mole^{-1}cm^{-1})	λ mμ	Ref.
Bromanil	2000	527	3
Chloranil	2500	518	3
Iodanil	1400	511	3
2,6-Dichloro-*p*-benzoquinone	2400	480	3
Chloro-*p*-benzoquinone	2000	442	3
1,2,3,5-Tetranitrobenzene	2300	425	4
p-Benzoquinone	2000	418	3
p-Toluoquinone	1800	409	3
1,2,4-Trinitrobenzene	1200	395	4
1,3,5-Trinitrobenzene	2500	395	4
Duroquinone	1200	393	3
2,6-Dimethyl-*p*-benzoquinone	2100	390	3
Iodine	8200	375	5
1,2,3-Trinitrobenzene	1500	350	4
Iodine monochloride	4000	334	5

[1] R. S. Mulliken, *J. Chem. Phys.* **19**, 514 (1951); *J. Amer. Chem. Soc.* **72**, 600 (1950); **74**, 811 (1952).
[2] H. McConnell, J. S. Ham and J. R. Platt, *J. Chem. Phys.* **21**, 66 (1953).
[3] R. Foster, D. Ll. Hammick and P. J. Placito, *J. Chem. Soc.* 3881 (1956).
[4] R. Foster, *J. Chem. Soc.* In press.
[5] L. J. Andrews and R. M. Keefer, *J. Amer. Chem. Soc.* **74**, 4500 (1952).

though differing much between themselves, gave complexes whose λ values were all within 20 mμ. It is now possible to list a similar set of data, namely for the complexes of various acceptors with hexamethylbenzene in carbon tetrachloride solution, in which the range of λ is ~190 mμ. There appears to be no correlation between λ and ε (Table 1). It is possible that any trend is masked by sterically bulky or asymmetrical groups in the acceptor molecule which would appear to lower ε while having little effect on λ. This behaviour is observed in donor molecules with a given acceptor; for example,[6] in dichloromethane, for the complex tetracyanoethylene-hexamethylbenzene, $\lambda = 545$ mμ, $\varepsilon = 4390$; whereas for tetracyanoethylene-hexaethylbenzene, $\lambda = 550$ mμ, $\varepsilon = 56$.

McConnell *et al.* were also able to show that the frequencies (ν) of charge-transfer band maxima for complexes of a series of donors with the acceptor iodine were proportional to the ionisation potentials (I) of the respective donors, thus:

$$\nu = a\mathrm{I} + b \tag{1}$$

and this was related to a theoretical expression:

$$\nu = \mathrm{I} - \mathrm{E} - \mathrm{W} \tag{2}$$

where E is the electron affinity of the acceptor molecule and W is the dissociation energy of the charge-transfer excited state. At the same time Hastings *et al.*[7] showed the relationship between ν for the complex and I for the donor molecule to be:

$$h\nu = \mathrm{I} - c_1 + \frac{c_2}{\mathrm{I} - c_1} \tag{3}$$

where $c_1 = \mathrm{E} + e^2/r - C_{AB}$, in which e^2/r is the coulomb attraction term and C_{AB} is the sum of all other energies; c_2 is a constant. Briegleb and Czekalla[8] have used such relationships to correlate ν for complexes of various donors with the electron acceptors: iodine, 1,3,5-trinitrobenzene and chloranil. There is good agreement between the values of ν and I's for the donor molecules. The absorption bands of complexes of chloranil with donors of accurately known ionization potential have now been remeasured in carbon tetrachloride solution and the values of ν plotted against Watanabe's[9] values of I for the donors (Fig. 1).

A reliable value for the naphthalene complex could not be obtained because of the coincidence of a fluorescence emission band of naphthalene with the charge-transfer absorption band of the complex. The least squares line gives a rather better fit than does the particular quadratic function proposed by Briegleb and Czekalla. It may be argued that some deviation should be expected because of the only approximate equality of the energy of the transition with the frequency of maximum absorption of a broad band. A maximum difference between the two correlations for chloranil complexes will be shown for complexes which have an absorption band at or about 700 mμ. For example perylene-chloranil in carbon tetrachloride has $\nu = 14200$ cm^{-1} (1·75 eV). The quadratic curve indicates 7·15 eV whilst the linear curve predicts 6·95 eV as the ionization potential of perylene, for which Hedges and Matsen[10] have calculated a value of 6·94 eV.

[6] R. E. Merrifield and W. D. Phillips, *J. Amer. Chem. Soc.* **80**, 2778 (1958).
[7] S. H. Hastings, J. L. Franklin, J. C. Schiller and F. A. Matsen, *J. Amer. Chem. Soc.* **75**, 2900 (1953).
[8] G. Briegleb and J. Czekalla, *Z. Electrochem.* **63**, 6 (1959).
[9] K. Watanabe, *J. Phys. Chem.* **22**, 1564 (1954); **26**, 184 (1957).
[10] R. M. Hedges and F. A. Matsen, *J. Chem. Phys.* **28**, 950 (1958).

Complexes formed from electron donors of low ionisation potential and acceptors of high electron affinity usually have favourable equilibrium constants and have the charge-transfer absorption bands at relatively long wavelengths often well separated from the absorption bands of the components themselves; this enables ν to be easily determined experimentally. Unfortunately neither electron affinities of aromatic acceptor molecules, nor ionisation potentials of many aromatic donor molecules of low ionisation potential have been measured. For this reason comparisons have been made of ν where either the donor or the acceptor is varied in a series of complexes.

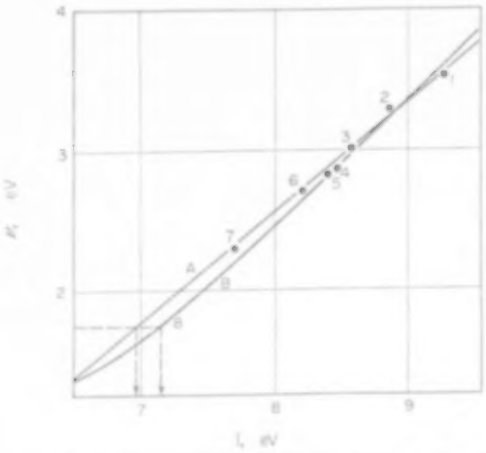

FIG. 1. Frequencies (ν) of charge-transfer bands of chloranil complexes of the donors: (1) benzene, (2) toluene, (3) *o*- and *m*-xylene, (4) *p*-xylene, (5) mesitylene, (6) anisole, (7) aniline, against the ionisation potentials (I) of these donors as correlated by (A) the least squares line (B) Briegleb and Czekalla's quadratic function. Two possible interpolated values of I for perylene are shown (8) (solvent carbon tetrachloride).

Consider the plots of $\nu_{1,y}$ of complexes of a given donor (1) with a series of acceptors (y) against $\nu_{2,y}$ of complexes of these acceptors with a second donor (2). It is implicit in equation (1) that these ν's will be related by a straight line of unit gradient provided that the parameter a in equation (1) is independent of the acceptor molecule. This condition appears to hold for the relatively strong complexes presently studied, viz.:

$$\nu_{2,y} = \nu_{1,y} + f \tag{4}$$

These are the complexes formed from the aromatic donors: hexamethylbenzene, N-methylaniline, N, N-dimethylaniline, N,N,N′,N′, tetramethyl-*p*-diaminodiphenylmethane (tetrabase), N,N,N′,N′, tetramethyl-*p*-phenylenediamine (Wurster's base), with the aromatic acceptors *m*-dinitrobenzene, 2,4,6-trinitrotoluene 1,3,5-trinitrobenzene, *p*-benzoquinone, chloro-*p*-benzoquinone, 2,6-dichloro-*p*-benzoquinone, chloranil. Certain other acceptors such as iodine and tetracyanoethylene were not included because of their irreversible action on the amines (but see below). All the spectra were measured in cyclohexane solution. Evans[11] has suggested that this may act as a donor, perhaps by promoting contact charge-transfer absorption[12] This does not appear to affect ν for the interactions studied which values correspond closely to

[11] D. F. Evans, *J. Chem. Phys.* **23**, 1424 (1955).
[12] L. E. Orgel and R. S. Mulliken, *J. Amer. Chem. Soc.* **79**, 4839 (1957).

those obtained in carbon tetrachloride solution. Use of the former solvent is advantageous in its greater transparency and in that complex formation is more favoured than in carbon tetrachloride.

The plots of equation (4) are given in Fig. 2. Equation (4), being linear, implies that a in equation (1) is independent of the particular acceptor: from Fig. 1, a may be taken as 0·85. Also, because of the linearity of equation (4), for a given donor, ν must be proportional to some function of the acceptor molecule which we may define as e in

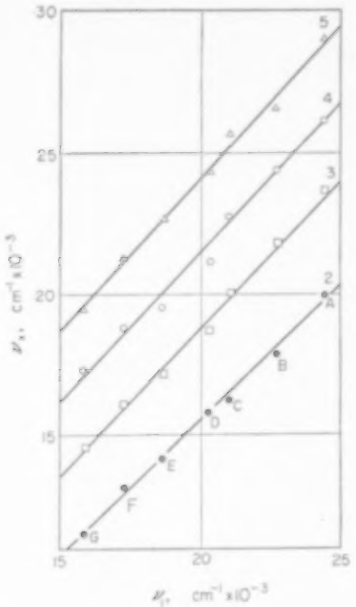

FIG. 2. Frequencies of the charge-transfer band (ν_x) of complexes of the donors: (2) Wurster's base, (3) tetrabase, (4) N-methylaniline, (5) hexamethylbenzene, with the series of acceptors: (A) *m*-dinitrobenzene, (B) 2,4,6-trinitrotoluene, (C) 1,3,5-trinitrobenzene, (D) *p*-benzoquinone (E) chloro-*p*-benzoquinone, (F) 2,6-dichloro-p-benzoquinone, (G) chloranil, against the frequencies of the charge-transfer bands (ν_1) of the complexes of these acceptors with N,N-dimethylaniline (solvent cyclohexane).

equation (5) and call the apparent electron affinity. This term e will include some measure of the bond dissociation energy W of equation (2).

All the present results may therefore be related by the equation:

$$\nu = 0{\cdot}85\,\mathrm{I} - e \qquad (5)$$

Selection of appropriate values of I and e to fit ν values of the complexes of the series of acceptors with one donor and the series of donors with one acceptor then enable the remaining ν's to be interpolated by equation (5) (Table 2).

The regularities, due to a in equation (1) being independent of the acceptor, cannot include the tetracyanoethylene complexes[6] (in dichloromethane) where $a = 0{\cdot}487$. The results for iodine complexes are conflicting: for polynuclear aromatics[13] $a = 0{\cdot}86$ (based on calculated I values), whereas for the iodine complexes related by McConnell *et al.*[2], $a = 0{\cdot}64$. Large deviations from straight lines of unit gradient in the plots of

[13] P. Bhattacharya and S. Basu, *Trans. Faraday Soc.* **54**, 1286 (1958).

TABLE 2. FREQUENCIES OF CHARGE-TRANSFER MAXIMA (ν)* OF COMPLEXES IN CYCLOHEXANE INTERPOLATED FROM THE IONIZATION POTENTIALS (I) OF THE DONORS AND THE APPARENT ELECTRON AFFINITIES (e) OF THE ACCEPTORS

(obtained from the complexes of donors with chloranil, and acceptors with N,N-dimethylaniline from equation (5), I(N,N-dimethylaniline) assumed to be 7·20 eV)

Measured values of ν in parentheses

Acceptor	Donor	Wurster's base	Tetrabase	N-Methyl-aniline	Hexamethyl-benzene
	I(eV) / e(eV)	6·67	7·05	7·38	7·67
2,6-Dichloro-*p*-benzo-quinone	4·36	1·59 (1·63)	1·97 (1·99)	2·30 (2·32)	2·59 (2·63)
Chloro-*p*-benzoquinone	4·19	1·76 (1·75)	2·14 (2·12)	2·47 (2·41)	2·76 (2·80)
Quinone	3·98	1·97 (1·95)	2·35 (2·31)	2·68 (2·62)	2·97 (3·01)
1,3,5-Trinitrobenzene	3·89	2·06 (2·01)	2·44 (2·48)	2·77 (2·81)	3·06 (3·18)
2,4,6-Trinitrotoluene	3·68	2·27 (2·21)	2·65 (2·69)	2·98 (3·01)	3·27 (3·28)
m-Dinitrobenzene	3·47	2·48 (2·47)	2·86 (2·92)	3·19 (3·23)	3·48 (3·59)

* Values are in eV.

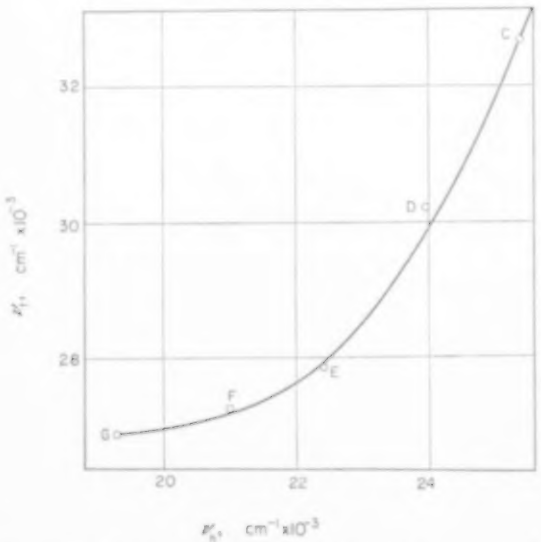

FIG. 3. Frequencies of charge-transfer bands (ν_T) of toluene complexes of a series of acceptors against the frequencies of the charge-transfer bands (ν_h) of the complexes of hexamethyl-benzene with the same series of acceptors (identified by the same letters as in Fig. 2) (solvent carbon tetrachloride).

equation (5) appear if the electron donor is only weakly effective. This is seen in the plot of ν for the complexes of the weak donor toluene (I = 8·82 eV) when plotted against ν for hexamethylbenzene complexes (Fig. 3).

EXPERIMENTAL

All melting points measured on a Kofler hot-stage.

Materials and solvents. Carbon tetrachloride and cyclohexane were B.D.H. spectroscopic grade, used without further purification.

Hexamethylbenzene. Prepared by Cullinane and Chard's method,[14] recrystallized five times from ethanol, m.p. 164°.

N,N-*Dimethylaniline.* B.D.H. AnalaR grade refluxed with acetic anhydride, washed five times with water, dried and distilled.

N-*Methylaniline.* B.D.H. AnalaR grade purified by the N-nitroso compound.

Tetrabase. Recrystallized four times from methanol, m.p. 91°.

Wurster's base. Prepared from the recrystallized dihydrochloride and distilled *in vacuo*, m.p. 51°.

m-*Dinitrobenzene.* B.D.H. analytical grade, recrystallized twice from carbon tetrachloride, m.p. 91°.

2,4,6-*Trinitrotoluene.* Recrystallized four times from carbon tetrachloride, m.p. 80·5°.

1,3,5-*Trinitrobenzene.* Recrystallized once from aqueous ethanol and thrice from carbon tetrachloride, m.p. 123°.

Chloro-p-*benzoquinone.* Prepared by Conant and Fieser's method,[15] recrystallized thrice from ethanol, m.p. 57°.

2,6-*Dichloro*-p-*benzoquinone.* Prepared by Faust's method,[16] recrystallized thrice from ethanol m.p. 120°.

Chloranil. Recrystallized four times from benzene, m.p. 289°.

Analytical. All spectra save those with absorption maxima at wavelengths longer than 720 mμ were measured on an Optica CF4 grating spectrophotometer. Above this wavelength a Unicam SP 500 was used. For each determination two basic solutions were made up: a solution 0·05–0·3 M of the donor, and a solution 10^{-3}–10^{-4} M of the acceptor. Equal volumes of these two solutions were mixed and two 1 cm fused silica cuvettes filled and placed *in tandem* in the cell compartment. In the compensating beam two cells were similarly placed, one containing the basic donor solution, the other the basic acceptor solution. The absorption measured is the difference between the unmixed and the mixed components; it is assumed that in the complex the charge-transfer band occurs in addition to the transition characteristic of the components. In most cases, because of the complexes selected, the charge-transfer band was at considerably longer wavelengths than the absorption of the components, but this technique enabled the band to be resolved in unfavourable cases. Determinations were repeated using different concentrations of donor and acceptor. All measurements were made at room temperature (18–20°).

In no case was any fine structure observed even with slit widths of 0·01 mm. This includes the spectra of the quinone–hexamethylbenzene complexes which we had previously claimed to possess fine structure.[3]

[14] N. M. Cullinane and S. J. Chard, *J. Chem. Soc.* **821** (1945).
[15] J. B. Conant and L. F. Fieser, *J. Amer. Chem. Soc.* **45**, 2204 (1923).
[16] A. Faust, *Liebigs Ann.* **149**, 153 (1869).

Tetrahedron, 1960, Vol. 10, pp. 102 to 106. Pergamon Press Ltd. Printed in Northern Ireland

ELECTRONIC SPECTRA OF ORGANIC MOLECULES AND THEIR INTERPRETATION—VI*

THE ELECTRONIC SPECTRA OF *p*-TERPHENYL AND ITS DERIVATES

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(*Received* 18 *March* 1960)

Abstract—This investigation deals with the effect of *para*-substituents on the positions observed in the high intensity bands (K-bands) of a *p*-polyphenyl series as the length of the conjugated system increases. The results obtained are interpreted in terms of the polarity and polarizability of the absorbing system. It is implicit in the discussion that a vinyl, or phenyl group behaves in the same manner as any of the other simple groups discussed.

INTRODUCTION

THE effect of substituents on the position of the absorption bands in the spectra of organic compounds is of considerable complexity, since it is dependent upon the location of the substituent within the absorbing system. The K-bands are best understood. There is general agreement that qualitatively they are due to transitions involving an electronic migration along the axis of the absorbing conjugated system.[1] Burawoy and Spinner[2] have shown that the position of a K-band is determined by two factors:

1. *The polarity of the absorbing system*

Influences such as terminal groups that increase the polarity of the absorbing system in the ground state facilitate the electronic migration, stabilize the excited state, and displace the K-band to longer wavelengths.

2. *The polarizability of the absorbing system*

The more polarizable the electrons of a terminal group are, the greater will be the displacement of the K-band to longer wavelengths.

According to this view the red-shift of the K-bands with the increasing number of conjugated linkages has to be attributed to the replacement of terminal C—H bonds by the more polarizable C—C=C group. It is known that this effect decreases with the increasing length of the absorbing conjugated system. If the terminal C—H group is replaced by any other substituent, i.e. a methyl group, chlorine atom or nitro group,

* Part V: *Tetrahedron* **5**, 340 (1959).
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[1] R. S. Mulliken, *J. Chem. Phys.* **3**, 522 (1935); **7**, 14, 21, 121, 339, 357, 395 (1939); G. N. Lewis and M. Calvin, *Chem. Rev.* **25**, 309 (1939); A. Burawoy, *Disc. Faraday Soc.* **9**, 70 (1950).
[2] A. Burawoy and E. Spinner, *J. Chem. Soc.* 2557 (1955).

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etc. the bathochromic effect should decrease with increasing length of the substituted conjugated system. However, in the case of a terminal vinyl or phenyl group, the first factor, i.e. any change of polarity of the absorbing system, is of little or no importance, and could be expected to become apparent only in the case of other, more polar terminal groups.

It was, therefore, thought to be of interest to test this view by investigating the differing effect of such polar terminal groups on the position of the K-band as the length of the substituted conjugated system increases. A series of *p*-substituted *p*-terphenyl compounds have been prepared and their spectra in ethanol and hexane determined. The results have been compared with those obtained from the corresponding benzene and diphenyl derivatives. This data can be seen in Table 1.

DISCUSSION

(a) *The effect of groups containing multiple bonds*

The displacement (D) observed on introducing a vinyl or a phenyl group in the *para* position of (benzene), diphenyl, and *p*-terphenyl decreases in both the (benzene) and diphenyl derivatives from 420–450 Å to 280–300 Å and finally to 170 Å (as shown by the spectrum of *p*-quaterphenyl in hexane). In contrast the red-shift of the K-band in benzaldehyde and in *p*-phenyl-benzaldehyde remains almost unchanged; the decreasing contribution of the polarizability of the substituent is balanced by the enhanced polarity (and resultant polarizability) of the second phenyl group in *p*-phenyl-benzaldehyde as compared with diphenyl itself. This interpretation is supported by the fact that the latter contribution is smaller in hexane than in ethanol, since the polarity of the molecule is smaller in the less polar solvent.

N-Methyl-benzaldimide and *p*-phenyl-N-methyl-benzaldimide show an intermediate behaviour, since the electron attracting power of the —C=N—Me group is greater than that of a vinyl group, but smaller than that of a carbonyl group. The effect of the —C=N—Me group is now smaller in the diphenyl derivative, but the decrease is definitely smaller than that observed for the vinyl group.

The behaviour of the powerful electron attracting nitro and cyano groups is similar to that of the carbonyl group. The displacement of the K-band is greater for *p*-nitrodiphenyl (585 Å) and *p*-cyanodiphenyl (215 Å) than in the corresponding benzene derivatives (565 and 205 Å). This displacement falls appreciably in the *p*-terphenyl derivatives (491 and 136 Å), but this decrease is less pronounced than that observed for *p*-phenyl substituent (447 → 283 → 170 Å). This indicates some small contribution caused by the induced polarity of the third phenyl group in the substituted terphenyl residue, since the polarity of the third phenyl group is to a lesser degree enhanced than that of the less distant second one in the diphenyl derivative.

(b) *The effect of "auxochromic groups"* (—OH, —OMe, —NH_2, —$\overline{O}$)

In hexane solution, the methoxyl group has a stronger bathochromic effect than a hydroxyl group. In ethanol, however, both groups behave similarly. Morton and Stubbs[3] were the first to show that this is due to the formation of an external hydrogen bond between the hydroxyl group and ethanol, which conclusion has also been confirmed by Burawoy and Chamberlain.[4] On introduction of these substituents into the

[3] R. A. Morton and A. L. Stubbs, *J. Chem. Soc.* 901, 920 (1934); 1347 (1940).
[4] A. Burawoy and J. T. Chamberlain, *J. Chem. Soc.* 2310 (1952).

Table 1. Maxima of K-bands in Å

X	Solvent	X–Ph	D	X–Ph·Ph	D	X–Ph·Ph·Ph	D
H	EtOH	2030[1] —	—	2475[6] 19,500	—	2769 32,000	—
	C_6H_{14}	2020[1] 6600	—	2467[6] 1900	—	2750 32,000	—
C_6H_5	EtOH	2475[6] 19,500	+445	2769 32,000	+294	— —	—
	C_6H_{14}	2467[6] 19,000	+447	2750 32,000	+283	2920[6] 55,000	+170
$H_2C{=}CH{-}$	EtOH	2453[7] 15,000	+423	2761 20,000	+286	— —	—
	C_6H_{14}	2451[7] 11,000	+431	2755 19,500	+288	— —	—
Me—N=CH—	EtOH	2450[7] 15,000	+420	2815 28,000	+340	— —	—
	C_6H_{14}	2420[7] 15,000	+400	2752 29,000	+285	— —	—
O=CH—	EtOH	2445[6] 13,500	+415	2895 23,000	+420	— —	—
	C_6H_{14}	2408[6] 1400	+388	2828 24,000	+361	— —	—
O_2N—	EtOH	2595[6] 9500	+565	3060 18,000	+585	3260 21,000	+491
	C_6H_{14}	2513[6] 9000	+493	2935 18,000	+471	3150 26,000	+400
$N^-{\equiv}C$—	EtOH	2235[7] 13,000	+205	2690 28,500	+215	2905 19,000	+136
	C_6H_{14}	2222[7] 17,000	+192	2665 21,000	+198	2865 25,000	+115
HO—	EtOH	2190[6] 5500	+160	2612[1] 22,500	+137	2890 31,000	+121
	C_6H_{14}	2118[6] 5500	+98	2548[6] 25,000	+81	2810 —	+60

[1] L. Doub and J. M. Vandenbelt, *J. Amer. Chem. Soc.* **69**, 2714 (1947).
[6] A. Burawoy and A. R. Thompson, *J. Chem. Soc.* 4314 (1956).
[7] A. Burawoy and J. P. Critchley, *Tetrahedron* **5**, 340 (1959).
[8] A. E. Gillam and D. H. Hey, *J. Chem. Soc.* 364 (1941).

TABLE 1—*continued*

X	Solvent	X–Ph	D	X–Ph·Ph	D	X–Ph·Ph·Ph	D
MeO—	EtOH	2195[a] 7500	+165	2610[a] 22,000	+135	2875 33,000	+106
	C_6H_{14}	2198[a] 7000	+178	2596[a] 27,000	+139	2854 34,000	+104
H_2N—	EtOH	2340[a] 8000	+314	2805 19,000	+330	3010 32,000	+241
	C_6H_{14}	2340[a] 7500	+320	2744 19,000	+277	2959 27,000	+209
O^-—	EtOH +0·1% NaOEt	2374[a] 12,500	+344	2970 23,000	+495	3270 33,000	+451
F—	EtOH	2068[a] 3000	+38	2462[a] 18,600	−13	2764 32,000	−5
	C_6H_{14}	2068[a] 3000	+48	2450[a] 16,000	−17	2737 31,000	−13
Cl—	EtOH	2130[a] 6100	+100	2550[a] 23,500	+75	2817 32,000	+48
	C_6H_{14}	2152[a] 9600	+132	2527[a] 20,500	+60	2782 34,000	+32
Br—	EtOH	2135[a] 7300	+105	2562[a] 25,500	+87	2832 34,000	+63
	C_6H_{14}	2160[a] 7700	+140	2540[a] 22,000	+73	2790 36,000	+40
I—	EtOH	2275[a] 12,000	+245	2586[a] 25,500	+111	2843 36,000	+74
	C_6H_{14}	2300[a] 11,000	+280	2573[a] 22,000	+106	2805 33,000	+55
H_3C—	EtOH	2065[a] 7000	+30	2520[a] 21,000	+45	2810 29,000	+41
	C_6H_{14}	— —	—	2513[a] 19,000	+46	2795 31,000	+45
H_3N^+—	EtOH/ conc. HCl 99:1	2030[a] 7500	−5	2483 19,000	+8	2800 33,000	+39

[a] These figures were determined with *water* as solvent, by Doub and Vandenbelt[2] who also give 2035 Å as the maximum for benzene in that solvent.
D = Increase of displacement by the substituent X compared with parent hydrocarbon.

[9] A. Burawoy and E. Spinner, *J. Chem. Soc.* 2085 (1955).

para position, the displacement of the K-bands of (benzene), diphenyl and *p*-terphenyl decreases in this order, but the overall percentage decrease is smaller than in the case of a vinyl group, which may indicate some contribution of the polarity factor. It is noteworthy that, although the position of the K-bands of both the phenols and the phenol ethers in ethanol is similar, the displacements fall off more appreciably in the case of the phenol ethers (165 → 135 → 106 Å) as compared with the phenols (160 → 137 → 121 Å). This effect can be explained on the basis of the electronic polarizability of the methoxyl group being greater than that of the hydrogen bonded hydroxyl group. This, in turn, is balanced by the greater electron repelling character of the latter group.

The amino group behaves similarly, but the greater electron repelling nature, and the resultant increased contribution of the polarity factor is shown by:

1. the greater red-shift in ethanol of the K-band of *p*-amino diphenyl (330 Å) compared with that of the K-band of aniline (314 Å).

2. the apparently more rapid fall of the displacement in the non-polar hexane (320 → 277 → 209 Å) than in the polar ethanol (314 → 330 → 241 Å).

The effect due to the increased polarity of the substituted system is convincingly demonstrated by the introduction of the powerful electron repelling negatively charged oxygen atom in the phenolate ions. The redshift is considerably greater in the *p*-phenyl-phenolate ion (495 Å) than in the phenolate ion itself (344 Å) and the displacement only slightly decreases in the ion of *p*-hydroxy-*p*-terphenyl (451 Å).

(c) *The effect of halogen atoms*

Burawoy and Thompson[6] have shown that the direction of the electron migration in the halogenobenzenes is towards the phenyl group (I):

This follows from the displacement of the K-bands to shorter wavelengths on replacing hexane by ethanol. The electron shift in the phenyl group due to the electron attracting terminal halogen atoms reduces the polarizability of the system away from the halogen atom, but this effect is masked by the opposing greater polarizability of the C—Hal electrons towards the carbon atoms (increasing in the order C—F < C—Cl < C—Br < C—I).

In contrast, the electron migration determining the stability of the excited state in the *p*-halogenodiphenyls is in the opposite direction (II) to that in the halogenobenzenes.

This is established by the opposing effect of solvents in these two series. The *p*-halogeno-diphenyls absorb at longer wavelengths in ethanol than in hexane. It is also supported by the fact that on introduction of the fluorine atom a blue shift results.

This shift is characteristic for all systems in which the fluorine atom is at the "receiving" end of the electronic migration, e.g. for *p*-fluoro aniline and *p*-fluorophenol.

This reversal of the solvent effect in the halogeno-substituted diphenyls as compared with the benzene derivatives is due to the electron shift in the ground state in the second C_6H_5—C group induced by the introduction of the halogen atom into the first phenyl group. This electron shift increases the polarizability of the system (C_6H_5—C_6H_4—Hal) towards the halogen atom and reduces it in the opposite direction i.e. a reversal of the relative polarizabilities of the overall absorbing system has occurred. The blue-shift due to the fluorine atom has been attributed to an appreciably smaller polarizability of the C-F electrons compared with those of the C—H bond.

The present investigation shows that, in agreement with these interpretations, the electronic migration in the *p*-halogeno-*p*-terphenyl series is in the same direction as that in the *p*-halogeno-diphenyls, i.e. towards the halogen atom. Again the fluorine is responsible for a blue shift and the K-band appears at longer wavelengths in the more polar ethanol than in hexane. As expected, the displacements are smaller than in the *p*-halogeno-diphenyls. However, the contribution of the polarity factor is indicated by the smaller decreases in ethanol as compared with that observed in hexane.

(d) *The effect of methyl and ammonium groups*

The effect of the methyl group is comparatively small, but as Burawoy and Spinner[9] have shown, the polarity factor is at least of the same degree as the polarizability of the C—CH_3 electrons. The former factor is responsible for the comparatively slight decrease of the red shift in the order of toluene > *p*-methyl-diphenyl > *p*-methyl-*p*-terphenyl.

The red shift due to the $\overset{+}{N}H_3$ group is greater in the *p*-terphenyl compound (31 Å) than in the diphenyl derivative (8 Å). Since it is known[6] that the polarizability of the C—$\overset{+}{N}H_3$ system is almost identical with that of the C—H bond, the observed displacement must be attributed to the increased polarity of the hydrocarbon system only. Thus, the third phenyl group in the *p*-terphenyl derivative, being more polar than in *p*-terphenyl itself, makes some contribution to the red-shift.

EXPERIMENTAL

The spectral determinations were carried out with a Hilger E3 quartz spectrograph fitted with a Spekker photometer, a tungsten-steel high tension spark being employed as the light source. All the investigated substances were obtained in a high state of purity. Most of the *p*-terphenyl compounds were prepared by the methods of France *et al.*,[10] *p*-cyano-, and *p*-fluoro-*p*-terphenyl have not been previously described.

p-*Fluoro*-p-*terphenyl*. *p*-Acetamino-*p'*-fluoro-diphenyl[11] (2 g) was dissolved in glacial acetic acid (100 cc) and acetic anhydride (20 cc) and phosphorus pentoxide (2·0 g) were added. The resultant solution was cooled to 10° and nitrous fumes (made from copper turnings and conc HNO_3) were passed into the cooled solution for 3 hr. The dark green solution was poured into water and the precipitated N-nitroso compound collected and dried under vacuum m.p. 85–86° (dec).

The dried unstable nitroso compound was allowed to react with dry benzene over a period of 3 days whence a brown tar formed and nitrogen was evolved. The tar was distilled under reduced pressure (10–3 mm) and *p*-fluoro-*p*-terphenyl (0·5 g) sublimed at 200°. The sublimate crystallizes from alcohol as colourless plates and needles of m.p. 214–215°. (Found: C, 86·8; H, 5·1. $C_{18}H_{13}F$ requires: C, 87·1; H, 5·2%).

[10] H. France, I. M. Heilbron and D. H. Hey, *J. Chem. Soc.* 1364 (1938).
[11] L. van Hove, *Chem. Zentr.* **1**, 312 (1923).

p-*Cyano*-p-*terphenyl*. *p*-Amino-*p*-terphenyl (0·5 g) was diazotized by the method of Pummerer and Bittner[12] and the diazo solution was added to a solution of potassium cuprocyanide (from 2 g copper sulphate). Nitrogen was evolved, and after 30 min the reaction mixture was heated to 50° on the steam bath. The precipitate formed was filtered off and extracted with ethanol and on cooling, *p*-cyano-*p*-terphenyl (0·1 g) crystallizes from alcohol as yellow platelets m.p. 219–220°. (Found: C, 89·1. H, 5·3; $C_{19}H_{13}N$ requires: C, 89·4; H, 5·1%).

Acknowledgements—Grateful acknowledgement is made to the Ministry of Education for the award of a maintenance grant (to P. B.) and to Mr. B. Manohin for the microanalyses carried out in connexion with this investigation.

[12] R. Pummerer and K. Bittner, *Ber. Dtsch. Chem. Ges.* **57**, 84 (1924).

Tetrahedron, 1960, Vol. 10, pp. 109 to 117. Pergamon Press Ltd. Printed in Northern Ireland

VOL. 10 1960

ELECTRONIC SPECTRA OF ORGANIC MOLECULES AND THEIR INTERPRETATION—VII*

THE EFFECT OF TERMINAL NITRO AND AMINO GROUPS ON THE ELECTRONIC SPECTRA OF CONJUGATED HYDROCARBON SYSTEMS

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(*Received* 11 *February* 1960)

Abstract—The effect of terminal nitro and amino groups of absorbing conjugated systems on the corresponding K-bands and, in particular, its dependence on the length of the substituted hydrocarbon system is discussed. It is confirmed that the position of a K-band is almost exclusively determined by the charge migration in one direction along the conjugated system. The interaction between a *p*-amino and a *p*-nitro group in the ground state of the *p*-nitro *p'*-amino derivatives of diphenyl, stilbene, and similar compounds (transmitted through the conjugated hydrocarbon system) decreases with the length of the conjugated system.

INTRODUCTION

PREVIOUS investigations by Burawoy[1] *et al.* have shown that the "effective" electronic migration along an absorbing system, as indicated by the long arrow in I, determines the transition energy, i.e. the position of the corresponding K-band. The contribution of the accompanying "complementary" electron migration in the opposite direction is only small and can generally be neglected in qualitative comparative discussions.

I. $A—(CH=CH)_n—B$ $\longrightarrow$

It has also been shown[1] that the displacement of a K-band to longer wavelengths on structural modification of the terminal groups (I, A–C or C–B) can be due to two factors:

(a) An electron shift (in the ground state) of the substituted system which will increase its electronic polarizability in the direction of the shift and facilitate the electronic migration.

(b) An increase of the electronic polarizability of the terminal group itself.

More recent experimental evidence[2] shows that the degree of stabilization of the excited state, i.e. the red shift of a K-band due to the perturbation not only by a terminal vinyl group, but also by any other substituent, decreases as the length of the substituted absorbing system increases.

This investigation deals, in greater detail, with the dependence of the effect of terminal nitro and amino groups (at both the electron receiving and electron donating end of the absorbing system) on the length of the substituted system. This involves the examination of a series of mono-*p*-nitro, mono-*p*-amino, *p*:*p'*-dinitro, *p*:*p'*-diamino, and *p*:*p'*-nitroamino-hydrocarbons such as benzene, diphenyl, terphenyl, quaterphenyl stilbene and tolane.

* Part VI: *Tetrahedron* **10**, 102 (1960).

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[1] A. Burawoy, *Tetrahedron* **2**, 122 (1958); A. Burawoy and E. Spinner, *J. Chem. Soc.* 2035, 2557 (1955); A. Burawoy and A. R. Thompson, *J. Chem. Soc.* 4314 (1956).

[2] P. Brocklehurst, A. Burawoy and A. R. Thompson, *Tetrahedron* **10**, 102 (1960).

DISCUSSION

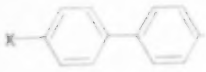
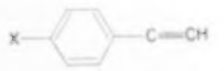
(a) *Spectra of* p*-nitro derivatives*

Data for the maxima and intensities of the K-bands of benzene, diphenyl, terphenyl, styrene, phenylacetylene, stilbene, tolane, and their *p*-mononitroderivatives in hexane and ethanol solutions are shown in Table 1, together with the displacements (D) due to the introduction of the nitro group.

The effective electronic migration of the transition corresponding to the K-band of the nitro derivatives is towards the nitro group as indicated by a long arrow in II.

It has already been shown[2] for the polyphenyl series that the introduction of the

TABLE 1. MAXIMA OF K-BANDS IN Å

Substance	Solvent	X = H		X = NO_2		D
		$\lambda_{max.}$ Å	$\Sigma_{max.}$	$\lambda_{max.}$ Å	$\Sigma_{max.}$	
	Ethanol	2030	—	2595	9500	565
	Hexane	2020	6600	2513	9000	493
	Ethanol	2475[a]	19,500	3060[a]	18,000	585
	Hexane	2467[a]	19,000	2935[a]	18,000	468
	Ethanol	2769[a]	32,000	3260[a]	21,000	491
	Hexane	2750[a]	32,000	3150[a]	26,000	400
	Ethanol	2453[a]	15,000	3010[a]	14,500	557
	Hexane	2450[a]	14,000	2895[a]	15,500	445
	Ethanol	2935	20,000	3400	17,500	465
	Hexane	2920	19,500	3325	19,500	405
	Ethanol	2346[a]	15,000			
		2444	13,500			
		2395[c]		2860[a]	15,000	465
	Hexane	2351[a]	15,500			
		2446	13,500			
		2398[c]		2798[a]	16,000	400
	Ethanol	2775	33,000			
		2960	29,000			
		2860[c]		3230	23,000	370
	Hexane	2775	34,000			
		2960	29,000			
		2860[c]		3200	25,000	340

C = centre of band system.

[a] A. Burawoy and J. P. Critchley, *Tetrahedron* 5, 340 (1959).

nitro group into benzene and diphenyl, to give nitrobenzene and *p*-nitrodiphenyl respectively, has similar effects on their spectra, because in the latter case the expected smaller displacement due to the decreasing contribution of the electronic polarizability

$$\text{II. Ar–NO}_2 \longrightarrow$$

of the C–NO_2 group is enhanced by the contribution of the electron-shift in the ground state of the second phenyl group in *p*-nitrodiphenyl.

In *p*-nitroterphenyl, however, the polar effect is transmitted to the third phenyl group to a much lesser degree. The bathochromic displacement due to the resultant electron-shift is now unable to make up for the reduced displacement caused by the decreasing contribution of the polarizability of the C–NO_2 system. Thus, the displacement observed is only 491 Å in ethanol, 400 Å in hexane compared with that in nitrobenzene (D = 565; 493 Å) and *p*-nitrodiphenyl (D = 585; 468 Å).

The effect of the nitro group in *p*-nitrostyrene (D = 557; 445 Å) is again similar to that observed for *p*-nitrodiphenyl (D = 585; 468 Å), but is somewhat smaller in *p*-nitrophenylacetylene (D = 465; 400 Å). Burawoy and Critchley[3] have shown that electron-shifts in triple bonds are responsible for smaller increases in the polarizabilities of these bonds than similar shifts in double bonds, and they attributed the reduced bathochromic effect of the nitro group (in *p*-nitrophenylacetylene) partly to this factor.

In *p*-nitrostyrene, the electron-shift caused by the nitro group results in an increase of the polarizability of the C—CH=CH_2 electron system towards the benzene ring and confers a slightly electron-repelling character to the vinyl group, whereas in *p*-nitrophenylacetylene the electron-attracting character of the —C≡CH group is preserved. Thus, the electron-attracting acetylene group is responsible for an electron-shift in the nitro group in opposition to the effective charge migration, i.e. a reduction in the polarity of the C–NO_2 group and consequently a reduction in its polarizability towards the oxygen atoms. This is an additional factor responsible for the reduced bathochromic effect of the nitro group in *p*-nitrophenylacetylene.

The bathochromic effect of the nitro group observed for *p*-nitrostilbene (D = 465; 405 Å) and *p*-nitrotolane (D = 370; 340 Å) in ethanol and hexane solutions is much less than the effect of the nitro group observed in the case of *p*-nitrostyrene (D = 557; 445 Å) and *p*-nitrophenylacetylene (D = 465; 400 Å) respectively. These observations are analogous to those made for *p*-nitroterphenyl. Again the polar effect caused by the introduction of the nitro group is transmitted to the additional phenyl group to a smaller degree.

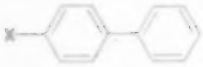
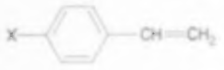
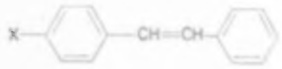
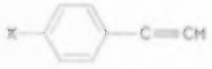
(b) *Spectra of* p-*amino derivatives*

Data for the maxima and intensities of the K-bands of the investigated hydrocarbons and their *p*-monoamino derivatives in hexane and ethanol solution, together with the displacements (D) due to the introduction of the amino group are shown in Table 2.

In the case of *p*-aminophenylacetylene, the electron-attracting acetylene group causes an electron-shift in the H_2N–C group which coincides with the direction of the effective charge migration. This is in contrast to *p*-nitro-phenylacetylene where the electron-attracting acetylene group causes an electronic-shift in the nitro group in

opposition to the effective charge migration. Thus, the effect of the nitro group in *p*-nitro-phenylacetylene is considerably smaller than in *p*-nitro-styrene, whereas the acetylene bathochromic displacement due to the introduction of the amino group is only slightly less for *p*-aminophenylacetylene than for *p*-aminostyrene.

Table 2. Maxima of K-bands in Å

Substance	Solvent	X = H		X = NH_2		D
		$\lambda_{max.}$ Å	$\Sigma_{max.}$	$\lambda_{max.}$ Å	$\Sigma_{max.}$	
	Ethanol	2030	—	2344	8000	314
	Hexane	2020	6600	2340	7500	320
	Ethanol	2475[a]	19,500	2805[a]	19,000	330
	Hexane	2467[a]	19,000	2744[a]	19,000	277
	Ethanol	2769[a]	32,000	3010[a]	32,000	241
	Hexane	2750[a]	32,000	2959[a]	27,000	209
	Ethanol	2453[a]	15,000	2770[a]	16,000	317
	Hexane	2450[a]	14,000	2728[a]	19,000	278
	Ethanol	2935	20,000	3180	18,500	245
	Hexane	2920	19,500	3150	24,000	230
	Ethanol	2346[a]	15,000			
		2444	13,500			
		3295[c]		2697[a]	20,500	302
	Hexane	2351[a]	15,500			
		2446	13,500			
		2398[c]		2650[a]	20,500	252
	Ethanol	2775	33,000			
		2960	29,000			
		2860[c]		3100	28,000	150
	Hexane	2775	14,000			
		2360	29,000			
		2860[c]		3010	28,000	150

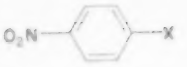
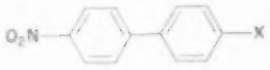
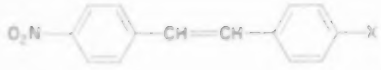
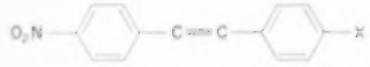
C = centre of band system.

Similar differences are observed for the corresponding stilbene and tolane derivatives.

(c) *Spectra of* p:p′*-dinitro and* p:p′*-diamino derivatives*

Data for the maxima and intensities of the K-bands of the *p*:*p*′-dinitro and *p*:*p*′-diamino derivatives of benzene, diphenyl, terphenyl, stilbene and tolane in ethanol solution, and the displacements on the introduction of the first (D) and of the second

TABLE 3

Substance	Solvent	X = H		X = NO_2		D	D′
		$\lambda_{max.}$ Å	$\Sigma_{max.}$	$\lambda_{max.}$ Å	$\Sigma_{max.}$		
	Ethanol	2595	9500	2061	13,000	565	+6
	Ethanol	3060[a]	18,000	3052	29,000	585	−8
	Ethanol	3260	21,000	3310	73,000	491	+50
	Ethanol	3400	17,500	3415	18,500	465	+15
	Ethanol	3230	23,000	3270	31,000	370	+40
	Dimethyl-formamide	—	—	3550	40,000	—	—

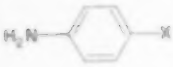
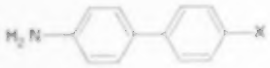
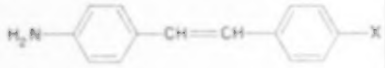
substituents (D′) are summarized in Tables 3 and 4. Many of the disubstituted derivatives were insoluble in hexane and therefore could not be investigated in this solvent (those of quaterphenyl are investigated in dimethyl formamide).

In the case of the nitro derivatives, the second electron attracting nitro group is at the electron-donating end of the effective charge migration, the direction of which is indicated by the long arrow in III.

III. $O_2N—(CH=CH)_n—NO_2$ ⟶

It is responsible for an electron-shift in the opposite direction to the effective charge

Table 4. Maxima of K-bands in Å

Substance	Solvent	X = H		X = NH_2		D	D′
		$\lambda_{max.}$ Å	$\Sigma_{max.}$	$\lambda_{max.}$ Å	$\Sigma_{max.}$		
	Ethanol	2344	8000	2440	11,000	314	+96
	Ethanol	2805[2]	19,000	2845	28,000	330	+40
	Ethanol	3010	32,000	3127	40,000	241	+117
	Ethanol	3180	18,500	3290	27,000	245	+110
	Ethanol	3100	28,000	3120	34,000	240	+20
	Dimethyl-formamide	—	—	3400	58,000	—	—

migration and, therefore, could be expected to cause a blue-shift of the K-band. This effect is balanced by the electronic polarizability of the C–NO_2 system towards the carbon atom, which should be considerably smaller than in the opposite direction. Thus negligible band displacements, to shorter or longer wavelengths, are observed on the introduction of the second nitro group.

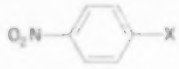
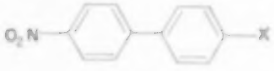
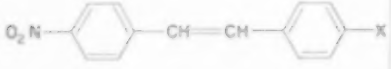
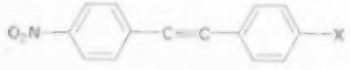
Similarly, the second electron-repelling amino group in the *p*:*p*′-diamino derivatives is responsible for an electron-shift in the opposite direction to the effective charge migration of the transition. This should cause a slight hypsochromic band displacement. However, the blue shift is masked by the effect of the polarizability of the

$C–NH_2$ electron system towards the amino group which is, again, smaller than in the opposite direction. This results in moderate displacements of the K-bands to longer wavelengths (20–117 Å) which may be compared with the much greater effect of the first amino group (240–314 Å).

(d) *Spectra of* p:p′*-nitroamino compounds*

The maxima and intensities of the K-bands of the *p*-nitro- and the *p*:*p*′-nitroamino derivatives of benzene, diphenyl, terphenyl, stilbene and tolane in ethanol solution

TABLE 5. MAXIMA OF BANDS OF *p*:*p*′-NITROAMINO DERIVATIVES (Å)

Substance	Solvent	X = H		X = NH_2		D	D′	D*
		$\lambda_{max.}$Å	$\Sigma_{max.}$	$\lambda_{max.}$Å	$\Sigma_{max.}$			
	Ethanol	2595	9500	3725	16,800	1130	314	816
	Ethanol	3060[a]	18,000	3775	13,800	715	330	385
	Ethanol	3200	21,000	3580	16,500	380	241	139
	Dimethyl-formamide	—	—	3400	37,000	—	—	—
	Ethanol	3400	17,500	4090	23,000	690	245	445
	Hexane	3325	19,500	3800	17,000	475	230	245
	Ethanol	3230	23,000	3890	18,500	660	240	420
	Hexane	3200	25,000	3640	19,500	440	150	290

and, as far as solubility allows, in hexane solution are shown in Table 5. (*p*:*p*′-Nitroaminoquaterphenyl is determined in dimethyl formamide.) The displacements (D) due to the introduction of the amino group into the nitrobenzene derivatives, the displacements (D′) observed on the introduction on the amino group into the corresponding hydrocarbons and the difference between these displacements (D*) are also shown.

The latter values (D*) give an approximate measure of the enhanced polarity resulting from the interaction of the terminal nitro and amino groups of the conjugated system.

It can be seen that the polarities of the systems will be much greater than those in the corresponding *p*-mononitro- and *p*-monoamino-derivatives respectively. The reinforced electron-shifts within the *p*:*p*′-nitroamino compounds coincide with the direction of the effective charge migration of the transition as indicated by the long arrow IV.

IV. $O_2N—(CH=CH)_n—NH_2$

They are responsible for increased electron polarizabilities and therefore large bathochromic displacements of the K-bands.

It is interesting to note that D* decreases in the order *p*-nitroaniline (816 Å) > *p*:*p*′-nitroaminodiphenyl (385 Å) > *p*:*p*′-nitroaminoterphenyl (139 Å). This clearly indicates that the interaction of the nitro and amino groups transmitted through the hydrocarbon system falls off rapidly with the increased length of the conjugated polyphenyl system.

Even more significant is the fact that the K-band, appearing at 3725 Å for *p*-nitroaniline, is only slightly displaced to 3775 Å for *p*:*p*′-nitroaminodiphenyl, and, in spite of the increased length of the conjugated system, undergoes blue-shifts for *p*:*p*′-nitroaminoterphenyl (3580 Å) and for *p*:*p*′-nitroaminoquaterphenyl (3400 Å). The bathochromic shift expected from the introduction of each additional phenyl group is cancelled in the terphenyl and quaterphenyl derivatives by the effect due to the decreasing interaction of the terminal amino and nitro groups.

In the case of the stilbene and tolane derivatives, the interaction of these groups is of the same order as observed for *p*:*p*′-nitroaminodiphenyl, in spite of the introduction of the additional vinyl and acetylene groups. This clearly indicates that the transmission of polar effects through aliphatic unsaturated groups is considerably greater than that through a phenyl group. It also shows that the transmission is of the same order for both double and triple bonds groups.

EXPERIMENTAL

The spectra were determined with a Hilger E3 quartz spectrograph fitted with a Spekker photometer, a tungsten-steel high-tension spark being employed as the source of light.

All the compounds were obtained in a high state of purity.

p-*Nitro*-p′-*amino-tolane*. Sodium hydrosulphide solution (prepared by dissolving sodium sulphide (2·4 g) in water (30 cc) and saturating with hydrogen sulphide) was added slowly with stirring to a suspension of finely powdered dinitrotolane[4] (3 g) in boiling ethanol (75 cc). The solution was refluxed for a further ½ hr and then allowed to cool. The reddish brown precipitate was filtered, and dried over calcium chloride in a vacuum desiccator. Crystallization from nitrobenzene afforded shining red plates of m.p. 210–211°. Yield: 1·6 g (61%). (Found: C, 69·7; H, 4·4; N, 11·9. $C_{14}H_{10}O_2N_2$ requires: C, 70·6; H, 4·2; N, 11·8%).

p-*Nitrotolane*. A solution of potassium hydroxide (0·65 g 2·5 moles KOH per mole dichloride) in ethanol (6 cc) and water (1 cc) was added dropwise during 10 min, with stirring, to a boiling solution of *p*-nitrostilbene dichloride[5] (1·3 g) in ethanol (20 cc). The solution was refluxed for a further ½ hr, cooled, and filtered to remove potassium chloride. Water (100 cc) was added to the mother liquor, and the solution was extracted with ether. The combined fractions were dried over anhydrous sodium sulphate. Removal of the solvent gave a yellowish-white solid (0·2 g 21%).

Crystallization from light petroleum (b.p. 60–80°) gave pale yellow microflakes of m.p. 121–122°. (Found: C, 75·3; H, 4·0; N, 6·5. $C_{14}H_9NO_2$ requires: C, 75·4; H, 4·0; N, 6·3%).

[4] P. Ruggli and F. Lang, *Helv. Chim. Acta* **21**, 38 (1938).
[5] P. Pfeiffer and S. Seriewakaja, *Ber. Dtsch. Chem. Ges.* **44**, 1108 (1911).

p-*Aminotolane*. Zinc dust (1 g) was added in small portions to a solution of *p*-nitrotolane (0·1 g) in ethanol (16 cc) with good stirring. Conc. HCl (4 g) was added dropwise, the temp. being maintained between 15–20° throughout the addition. Stirring was continued for 2·5 hr, and the solution filtered. Dil. H_2SO_4 (25%, 5 cc) was added to the filtrate and a white precipitate of *p*-aminotolane sulphate separated. Basification with sodium hydroxide solution afforded a white precipitate. Crystallization from aqueous ethanol gave white needles m.p. 127–128°. (Yield: 0·05 g 58%). (Found: C, 87·4; H, 5·6; N, 7·1. $C_{14}H_{11}N$ requires: C, 87·0; H, 5·7; N, 7·3%).

p-*Nitro*-p′-*aminoterphenyl*. *p*:*p*′-Dinitroterphenyl[6] (8 g) was dissolved in pyridine (200 cc) and a solution of crystalline sodium hydrosulphide [made by saturating a solution of crystalline sodium sulphide (5·3 g) in water (20 cc) with hydrogen sulphide] was added during 15 min at the boil. The reaction mixture was refluxed for a further 15 min. Removal of the pyridine by distillation, the last portion under reduced pressure, afforded an orange-brown solid. (Yield: 6·5 g 92·7%). Crystallization from nitrobenzene gave golden plates m.p. 304°. (Found: C, 73·9; H, 4·8; N, 9·5. $C_{18}H_{14}N_2O_2$ requires: C, 74·4; H, 4·8; N, 9·6%).

p:p′-*Diaminoterphenyl*. A solution of sodium hydrosulphide [made by saturating a solution of crystalline sodium sulphide (5·5 g) in water (20 cc) with hydrogen sulphide] was added to a boiling solution of *p*:*p*′-dinitro-terphenyl[6] (4 g) in pyridine (200 cc) and the mixture was refluxed for 2 hr. Removal of the pyridine by distillation, the last portion under reduced pressure, afforded a yellow solid. Crystallization from ethanol gave yellow plates of m.p. 242–243°. (Yield: 2·4 g 80%). (Found: C, 83·3; H, 6·3. $C_{18}H_{16}N_2$ requires: C, 83·1; H, 6·4%).

p-*Nitro*-p′-*amino*-*quaterphenyl*. A solution of crystalline sodium sulphide (1·1 g) in water (20 cc) was saturated with hydrogen sulphide and pyridine (20 cc) added to the solution. *p*:*p*′-Dinitroquaterphenyl[7] (2 g) was dissolved in pyridine (200 cc) and heated to the boil. The hydrosulphide was added over ½ hr and the mixture was allowed to boil for a further ½ hr. Excess pyridine was then distilled off, the final traces being removed under reduced pressure. The product so obtained was crystallized from dimethylformamide as red-brown plates of m.p. 345° dec. (Yield: 1·1 g 61%). (Found: C, 81·0; H, 5·2; N, 7·6. $C_{24}H_{18}N_2O_2$ requires: C, 80·9; H, 5·1; N, 7·8%).

Acknowledgements—Grateful acknowledgement is made to the Department of Scientific and Industrial Research for the provision of a maintenance grant for one of us (R. W. H. B.) and to Mr. B. Manohin for the microanalyses carried out in connexion with this investigation.

[6] H. France, I. M. Heilbron, and D. H. Hey, *J. Chem. Soc.* 1364 (1938).
[7] J. Harley-Mason and F. G. Mann, *J. Chem. Soc.* 1379 (1940).

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Tetrahedron, 1960, Vol. 10, pp. 118 to 124. Pergamon Press Ltd. Printed in Northern Ireland

ELECTRONIC SPECTRA OF ORGANIC MOLECULES AND THEIR INTERPRETATION—VIII*

THE ELECTRONIC SPECTRA OF THIOBENZOPHENONE AND ITS DERIVATIVES

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(*Received* 18 *March* 1960)

Abstract—The effect of the hydroxyl, methoxy, dimethylamino groups as well as the charged O^- atom at the end of the conjugated system (I) of thiobenzophenone on the positions of the corresponding K-bands and R-bands is discussed.

(I) p-X—C_6H_4—C(Ph) = S X = HO, MeO, NMe_2, and $\bar{O}$

THE effect of substituting the previously mentioned groups in the *para* position of the unsubstituted phenyl group (i.e. in the side chain of the main conjugated system) on the R-bands and K-bands is also discussed and shown to be similar.

The direction of the electronic transition in the excited state in the side-chain phenyl group of the conjugated system is shown to be away from the thiocarbonyl group.

INTRODUCTION

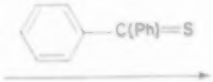
Although the electronic spectra of a considerable number of organic compounds have been determined and reported in the literature, the data (mostly incomplete) for only a few thioketones is available.

It was considered, therefore, that a systematic examination of the ultra-violet spectra of these compounds would produce information about several aspects of the electronic spectra of organic compounds, such as the similar effect of side-chain substituents on the positions of K-bands and R-bands, and the effect of substituents on the position of R- and K-bands in general.

1. *The spectrum of thiobenzophenone*

The spectrum of thiobenzophenone in ethanol shows three regions of absorption:

(i) A K-band of fairly high intensity (λ_{max} Å 3165 ε_{max} 15,600) which originates in a transition involving an electronic migration along the conjugated system as indicated in (a).

(a) 

(ii) An R-band of low intensity (λ_{max} Å 5990 ε_{max} 185) characteristic of the thiocarbonyl group.

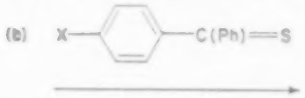
* Part VII: *Tetrahedron* **10**, 109 (1960).
† Present address: Basic Research Department, Thomas Hedley, City Road, Newcastle upon Tyne, 1.

(iii) An absorption band at much shorter wavelengths (λ_{max} Å 2350 ε_{max} 9000), the origin of which is uncertain.

The B-band[1] corresponding to the 2600 Å band system of benzene is not observed as it is masked by the K-band absorption of higher intensity. The K-band (as will be shown later) must be considered as arising from the two equivalent electronic transitions along the two conjugated systems present in the molecule.

2. *K-bands*

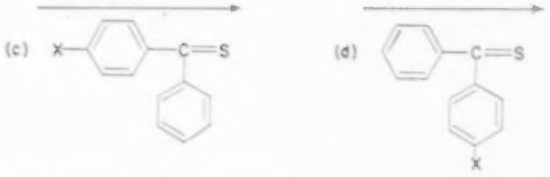
(i) *The effect of terminal groups of the conjugated system.* The K-band of thiobenzophenone in ethanol is displaced to longer wavelengths in the spectra of *p*-methoxy, *p*-benzyloxy, *p*-hydroxy, *p*-dimethylamino, *p*-phenylthiobenzophenone, and the sodium salt of *p*-hydroxythiobenzophenone. (Table 1). The substituents in the *para* position to the thio-carbonyl group are terminal groups of the absorbing conjugated system (b):



Recent work[2] has shown that the effect of such groups on the position of the K-band are twofold. The K-band is displaced to longer wavelengths as the length of the absorbing system is increased, i.e. more precisely, as the *polarizability* of the electrons of the terminal group increases. The higher this polarizability becomes, the greater is the displacement to longer wavelengths. Secondly, as the *polarity* of the absorbing system is increased, the greater is the displacement of the K-band concerned to longer wavelengths. Influences that increase the polarity of the substituted system facilitate the electron migration and stabilize the excited state.

The former factor is predominant in *p*-phenyl-thiobenzophenone whereas, in the *p*-hydroxy-, and *p*-amino-substituted derivatives the increased polarity of the absorbing system makes a large contribution. This would account for the much greater effect of the *p*-dimethylamino group and the negatively charged oxygen atom compared with the *p*-hydroxyl, and alkoxyl groups.

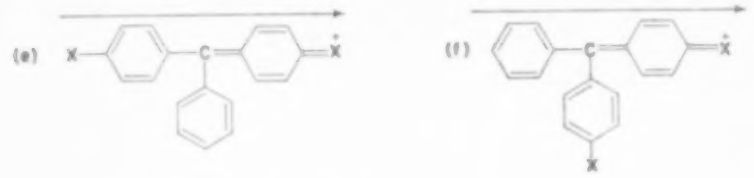
(ii) *Secondary K-bands.* Thiobenzophenone contains two equivalent conjugated systems, both making a contribution to the observed K-band. If, however, one of the *para* positions only is substituted, the two absorbing conjugated systems become unequal, and hence two K-bands could be expected, resulting from the different electronic systems (c) and (d). They should be observable if the bands are sufficiently separated.



The spectra of the investigated *p*-mono-substituted thiobenzophenone derivatives show either two separated K-bands or an inflexion superimposed on the more

[1] E. A. Braude, *Ann. Rep. Chem. Soc.* **42**, 105 (1945).
[2] A. Burawoy and E. Spinner, *J. Chem. Soc.* 2557 (1955); A. Burawoy, J. P. Critchley and A. R. Thompson, *Tetrahedron* **4**, 403 (1958).

pronounced K-band at longer wavelengths. Their maxima are given in Table 1 where they are denoted as K_1 and K_2 bands. This is analogous to earlier observations[3] that the spectra of *p*:*p*′-disubstituted triphenyl-methyl cations show two K-bands which can be attributed to transitions involving an electronic migration along the axes of the two conjugated systems present (e) and (f).



where X = OH, OMe, NMe_2, SMe

TABLE 1. MAXIMA OF K-BANDS OF COMPOUNDS X—C(Ph)═S IN ETHANOL

Substituent X—	K_1-Band		K_2-Band	
	max Å	max	max Å	max
H—	3165	15,600	—	—
CH_3O—	3595	12,100	3220	9000
$C_6H_5CH_2O$—	3610	17,000	3210	12,400
HO—	3685	16,000	3175	10,800
Me_2N—	4390	23,600	3320	10,400
$\bar{O}$—	4500	32,600	3060	6600
C_6H_5—	3545	17,800	3370	inflexion

(iii) *The effect of side-chain substituents of conjugated systems.* Substituents (in the *para* position) such as phenyl, hydroxyl, methoxyl, dimethylamino, and the anion $\bar{O}$ as terminal groups of the absorbing conjugated system displace the K-band of thiobenzophenone to considerably longer wavelengths. If, however, a second substituent is introduced into the unsubstituted phenyl group (representing a branch of the conjugated system) only a small effect is observed. Thus the K-band of *p*:*p*′-diphenyl-thiobenzophenone appears at only slightly longer wavelengths than the K_1-band of the *p*-phenyl-thiobenzophenone (Table 2). Similarly, the K-bands of *p*:*p*′-dimethoxy, *p*:*p*′-dihydroxy-, and *p*:*p*′-tetramethyldiaminothiobenzophenones as well as the sodium salt of *p*:*p*′-dihydroxy-thiobenzophenone absorb at slightly shorter wavelengths than the corresponding mono-substituted derivatives (Table 2). Similar observations have been made by Burawoy[3] in the di- and tri-substituted triphenyl-methyl cations. Moreover, since the two absorbing conjugated systems in the *p*:*p*′-disubstituted thiobenzophenones are once more equivalent, only *one* K-band of increased intensity is now observed.

It is also of interest that the K_2-bands of all the investigated mono-substituted thiobenzophenones appear at similar wavelengths to the K-band of thiobenzophenone

[3] A. Burawoy, *Ber. Dtsch. Chem. Ges.* **66**, 228 (1933); G. N. Lewis and J. Bigeleisen, *J. Amer. Chem. Soc.* **65**, 2102 (1943).

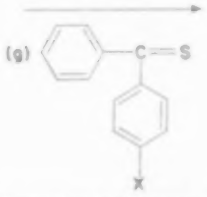
TABLE 2. MAXIMA OF K-BANDS OF COMPOUNDS X—C(=S)—Y IN ETHANOL

Substituents		K_1-Band		D	K_2-Band	
p-X	*p'*-Y	max Å	max	Å	max Å	max
MeO	H	3595	12,100		3220	9000
MeO	MeO	3525	20,000	−75	—	—
HO	H	3685	17,000		3170	12,400
HO	HO	3595	24,000	−90	—	—
Me_2N	H	4390	23,600		3320	10,400
Me_2N	Me_2N	4330	37,000	−60	—	—
$\bar{O}$	H	4500	32,600		3060	6600
$\bar{O}$	$\bar{O}$	4440	36,000	−60	—	—
C_6H_5	H	3545	17,800		3370	inflexion
C_6H_5	C_6H_5	3568	25,000	+23	—	—

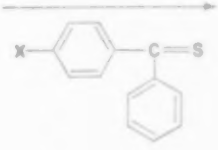
D = displacement of K_1-band due to substituent in the side-chain.

itself (Table 2). The substituted phenyl group, in this case, is the side-chain of the absorbing system and, thus, the substituent has only a small effect.

The effect of side-chain substituents on the position of the K-bands should involve the same two factors that are responsible for the effect of terminal groups. They will cause changes in the polarity of the substituted system in the ground state, resulting in changes of its polarizability, and they will participate in the electronic migration of the transition. These factors will now be of greater complexity. Thus, in the substances investigated, an electron repelling group such as OMe, NMe_2, or $\bar{O}$ [as substituent X in (g)] will cause electron displacements in the ground state towards both the aryl and thio-carbonyl groups. This will inhibit the electron migration of the transition as indicated in (g) in the former, and facilitate it in the latter part of the principal absorbing system.



Transition inhibited by X



Transition facilitated by X.

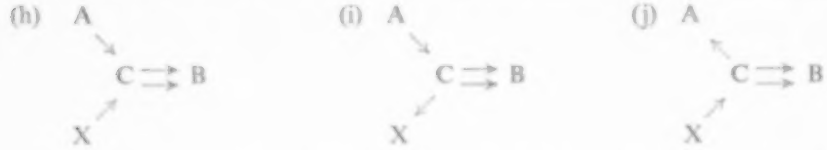
It is probable that the hypsochromic displacement by these side-chain groups arises from a somewhat greater effect in the Ar—C bond than in the C=S linkage. The participation of the electrons of the side-chain in the electronic migration of the transition will also make some contribution, but the resultant effect should be rather complex and would need more extensive investigation.

However, the observations of two K-bands in the mono-substituted compounds indicates that in the excited state the direction of the electronic migration in the side-chain phenyl group is away from the thiocarbonyl group.[4]

[4] A. Burawoy, *Ber. Dtsch. Chem. Ges.* **63**, 3164 (1930); *Tetrahedron* **2**, 122 (1958).

In a system such as A—C(X)=B, in which the effective electronic migration is directed from A towards B, a migration in the branch C—X towards the carbon atom would allow for only *one* electronic transition (h). In the alternative case, two similar electronic transitions (i and j) could be expected. They would be responsible for two K-bands, which in favourable conditions could be observed.

This is indeed the case in the *p*-substituted thiobenzophenones and in the *p*:*p'* substituted-triphenyl-methyl ions. When two *para* substituents are present branches A



and X become equivalent and only one K-band of high intensity is observed. This does not exclude the possible existence of a K-band corresponding to excited state (h) at considerably shorter wavelengths.

3. *R-Bands*

As previously shown by Burawoy[4], the observations related to R-bands can be reduced to two simple generalisations:

(a) Substituents of the chromophoric double bonds have the same qualitative effects on R-bands as substituents (in a side-chain) of an absorbing system on K-bands.

(b) R-Bands are displaced to shorter wavelengths by influences (solvent effect, proton addition, substituents, hydrogen-bond formation) which increase the polarity of the chromophoric double bond.

The considerable separation of the R- and K-bands in the spectra of thiobenzophenone and its derivatives allows, amongst other effects, a comparison of the effect of substituents on both R- and K-bands in the same molecule. This is in contrast to the ketones and azo compounds where the separation of the bands is usually incomplete, the R-band being partly or completely masked by the more intense K-band.

Data for the effect of substituents on the position of the R-band of thiobenzonone are summarized in Table 3 and compared with the effects of these substituents on the K-bands.

It can be seen from Table 3 that the displacement of the R-band to shorter wavelengths increases with the increasing electron donating character of the substituent, i.e. in the order H < OMe(OH) < NMe_2.

The effect of phenyl groups introduced into the *para*-positions of thiobenzophenone is quite characteristic. Whilst the K-band in *p*-phenyl-thiobenzophenone is displaced appreciably to longer wavelengths (by 380 Å) by the first phenyl group, the R-band is only slightly displaced to longer wavelengths (+15 Å). But, because the second *p*-phenyl substituent in *p*:*p'*-di-phenylthiobenzophenone is in the side-chain of the absorbing conjugated system it is again responsible for a slight shift of the R-band to longer wavelengths (+20 Å) and a slight displacement of the K-band to longer wavelengths (+23 Å). This shift is negligible compared with the displacement of the K-band to longer wavelengths caused by the first phenyl group.

When a *p*-hydroxy group is substituted into thiobenzophenone the K-band is displaced to longer wavelengths (+520 Å) and the R-band to shorter wavelengths

TABLE 3. EFFECT OF SUBSTITUENTS ON R- AND K-BANDS OF THIOBENZOPHENONE (IN ETHANOL)

Substituents		R-Band		D	K_1-Band		D
p-X	*p*-X′	max Å	max	Å	max Å	max	Å
H	H	5990	185	—	3165	15,600	—
H	HO	5800	254	−190	3685	16,000	+520
HO	HO	5662	370	−128	3595	25,000	+430
CH_3O	H	5800	175	−190	3595	12,100	+430
C_6H_5-CH_2O	H	5875	275	−115	3610	17,000	+445
CH_3O	CH_3O	5770	288	−120	3580	20,000	+415
$(CH_3)_2N$	H	5475	452	−515	4390	23,600	+1225
$(CH_3)_2N$	$(CH_3)_2N$	inflexion	—	—	4330	37,000	+1165
C_6H_5	H	6005	246	+15	3545	17,800	+380
C_6H_5	C_6H_5	6025	318	+35	3568	25,000	+403

D = Displacement due to substituent

(−190 Å). When a second hydroxyl group is substituted in the vacant *para*-position (i.e. in the side-chain of the absorbing system) the displacements observed (compared with thiobenzophenone) are −128 Å for the R-band, and +430 Å for the K-band. Compared with *p*-hydroxythiobenzophenone, therefore, both bands are displaced towards their original positions in thiobenzophenone when the second hydroxyl group is substituted in the side-chain, the R-band by (190–128 Å) 62 Å, and the K-band by (520–430 Å) 90 Å. Similar results obtain for the *p*-methoxy substituted compounds but unfortunately the data for the *p*-dimethylamino substituted compounds is incomplete due to the inflexion observed in the R-band of *p*:*p*′-dimethylamino-thiobenzophenone.

These observations confirm that the effect of substituents of the chromophoric double bond on the position of the R-bands is similar to that of these substituents (in a side-chain) of the absorbing system on K-bands.

EXPERIMENTAL

All the spectra included in this publication were determined using a Hilger Uvispek Photoelectric Spectrophotometer. All the compounds were obtained in a high state of purity. *p*-Hydroxy, *p*:*p*′-dihydroxy, *p*-methoxy, and *p*-benzyloxy thiobenzophenones have not been previously described.

p-*Hydroxy-thiobenzophenone*. *p*-Hydroxybenzophenone (5·0 g) dissolved in ethanol (50 ml) was treated with dry hydrogen chloride and hydrogen sulphide for 3 days. The thioketone precipitated as red plates on pouring the reaction mixture into water. The compound was crystallized from a 1:1 mixture of chloroform and pet ether (b.p. 60–80°), m.p. 139°. Yield: 4·3 g; 78%. (Found: C, 73·0; H, 4·6; $C_{13}H_{10}OS$ requires: C, 73·1; H, 4·67%).

p:p′-*Dihydroxythiobenzophenone*. *p*:*p*′-Dihydroxythiobenzophenone (5·0 g) was dissolved in ethanol (50 ml) and treated with dry hydrogen chloride and hydrogen sulphide for 3 days. The thioketone precipitated as red plates when the reaction mixture was poured into water. The compound was crystallized from water giving red plates and needles of the monohydrate (m. p. 114° dec). After drying over phosphorus pentoxide *in vacuo*, the thioketone had a m.p. 190°. Yield: 4·5 g; 83%. (Found: C, 68·1; H, 4·3; $C_{13}H_{10}O_2S$ requires: C, 67·8; H, 4·4%).

p-*Methoxy-thiobenzophenone*. *p*-Methoxybenzophenone (5·0 g) was dissolved in ethanol (50 ml) and treated with dry hydrogen sulphide and hydrogen chloride for 3 days, and the reaction mixture then poured into water. A blue oil separated which was extracted with ether. After drying over anhydrous sodium sulphate and removal of the ether, a viscous blue oil remained which resisted all attempts to purify it. The sample was finally used for spectral determination without further purification. (Found: C, 72·5; H, 5·4; $C_{14}H_{12}OS$ requires: C, 73·7; H, 5·3%).

To overcome this difficulty, *p*-benzyloxythiobenzophenone was prepared, its spectra determined, and the figures used throughout the discussion. No appreciable difference was observed between the spectra of *p*-methoxy, and *p*-benzyloxythiobenzophenone.

p-*Benzyloxythiobenzophenone*. *p*-Benzyloxybenzophenone (5·0 g) was dissolved in ethanol (50 ml) and dry hydrogen sulphide and hydrogen chloride passed in. After 10 hr the thioketone crystallized out as blue plates which on recrystallization from ethanol had m. p. 110–111°. Yield: 4·3 g: 90%. (Found: C, 79·2; H, 5·3. $C_{20}H_{16}OS$ requires: C, 78·9; H, 5·3%).

p:p′-*Diphenyl-thiobenzophenone*. *p*:*p*′-Diphenylbenzophenone (2·0 g) was refluxed for 10 hr with phosphorus pentachloride (5·0 g) in toluene (10 ml). The reaction mixture was distilled under reduced pressure to remove the toluene and phosphorus oxychloride. The residual keto-dichloride was dissolved in dry light petroleum (b. p. 60–80°, 50 ml) and refluxed with thioacetic acid (14 g) for 30 min. *p*:*p*′-Diphenylthiobenzophenone crystallized out and was filtered off. On recrystallization from pet ether (b. p. 100–120°) blue plates m. p. 189° were obtained (Schönberg *et al.*[5] give m.p. 228°). Yield: 1·2 g 56%. (Found: C, 86·0; H, 5·0. Calc. for $C_{25}H_{18}S$. C, 85·7, H, 5·1%).

[5] A. Schönberg, O. Schutz and S. Nickel, *Ber. Dtsch. Chem. Ges.* **61**, 2175 (1928).

Tetrahedron, 1960, Vol. 10, pp. 125 to 126. Pergamon Press Ltd. Printed in Northern Ireland

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BOOK REVIEWS

CARL S. MARVEL: **An Introduction to the Organic Chemistry of High Polymers.** John Wiley, New York; Chapman & Hall, London, 1959. 82 pp., $4.50.

THIS book is an outgrowth of a series of notes compiled by the author for the "Humble Lectures in Science" in June, 1956. As the author states, they were intended to be used by the beginner in polymer synthesis. As such, the book is most useful.

Although the book is only 82 pages, it covers a wide range of topics but, of more importance, it covers most of the important ones. The material on diene polymerization and new ionic systems includes a good summary of recent material.

This is the type of book that could be used for a month's work in an organic course for seniors majoring in chemistry very profitably, or as a source of examples for the standard undergraduate organic chemistry course. I would urge that every student who intends to do graduate work in organic chemistry have this book available to him.

C. G. OVERBERGER

R. T. MORRISON and R. N. BOYD: **Organic Chemistry.** Allyn and Bacon, Boston, Mass., 1959, xiv + 948 pp., $10.75.

IT is clear that the pedagogy of elementary organic chemistry is in a state of flux. The year course for majors has no hope of achieving the encyclopedic envelopment of organic chemistry of a generation ago. But more difficulty has been experienced in the development of any general agreement regarding the amount of theoretical interpretation to be included and the level of erudition of that presented.

Professors Morrison and Boyd are to be commended for this most recent effort in this direction. They have made a valuable contribution to the teaching of elementary organic chemistry. The early portion of the book introduces a variety of concepts very rapidly: for example, free radicals (p. 35), chain reactions (p. 37), bond dissociation energies (p. 39), activation energy (p. 41), reaction co-ordinate (p. 42), temperature coefficient of rate of reaction (p. 47), and conformations (p. 60). These concepts are not introduced in a vacuum, but are rather related to specific situations. Of further importance is their continued use throughout the remainder of the book. Liberal use is made of reaction co-ordinate-energy diagrams, including the Hammond postulate. The exposition is clear, and a great deal of care has been taken to provide a "teaching" framework for the material included. Experimental facts and derived interpretive conclusions are carefully distinguished. At the end of each chapter a long problem set of graded difficulty is included, with structure determinations and synthetic sequences based in many instances upon actual experimental data. Answers are also given for some of the problems. The amount of material from the very recent literature is impressively large. The authors have made a valuable contribution in reducing the "lead time" from the research laboratory to the elementary course.

Apparently, any reviewer feels compelled to comment on typography. The book seems remarkably free of errors. Only one (α instead of β, p. 626) came to the reviewer's attention. There is a use of the term "hindered rotation" (p. 104) which has an unfortunate connotation.

Naturally certain aspects of the sequence of material presented seem less than optimum to any individual. It is unfortunate that the detailed discussion of the preparative utility of diazonium salts is left to p. 571 in an integrated text, and that the reactions of the Grignard reagent are delayed so long. But these are matters of personal preference, and in no way detract from this excellent presentation of organic chemistry with full cognizance of modern theory.

D. S. NOYCE

CARL DJERASSI: **Optical Rotatory Dispersion, Applications to Organic Chemistry (McGraw-Hill Series in Advanced Chemistry).** McGraw-Hill, New York, 1960. 293 pp., $6.50.

AMONG the physical methods used by the organic chemist for the solution of his problems polarimetry is one of the oldest. However, with very few exceptions the determination of optical rotation in organic laboratories was limited to one wavelength only; that of the sodium *D* line. It is chiefly the merit of Carl Djerassi to have clearly recognized the serious shortcomings of this monochromatic procedure and the advantages of determining optical rotations in the entire region between the sodium *D* line and the ultra-violet.

Since, prior to Djerassi's work, hardly any data were accumulated, it was necessary for this author to amass a large amount of experimental material in his own laboratory in order to draw the necessary generalizations and outline the principal uses of optical rotatory dispersion in organic chemistry. It is to be welcomed that a coherent account of this monumental work has now been made available in book form by the principal exponent of the method himself.

The book starts with a simple and very readable explanation of the "Cotton effect" and the Drude equation. A short section on nomenclature and a chapter on instrumentation follow. The largest amount of rotatory dispersion studies performed up till now was on carbonyl compounds, and among these the steroids provided the most advantageous field for the initial exploration. Chap. 4 deals in detail with the uses of rotatory dispersion in the determination of structure and configuration of steroid ketones. A discussion of bicyclic ketones and triterpenoids follows in Chap. 5 and 6. The Chap. 7 on monocyclic ketones and aldehydes shows very clearly that rotatory dispersion will eventually become a very important tool for the solution of conformational problems in flexible molecules.

Of great interest is Chap. 9 on haloketones, which discusses among other topics, the application of Djerassi's axial haloketone rule. This rule provides one of the means to determine absolute configuration by rotatory dispersion. The general problem of absolute configuration is discussed in Chap. 10 and it is one of the most important uses of rotatory dispersion in organic chemistry.

The theory of rotatory dispersion curves is treated in an excellent chapter (12) written by A. Moscowitz, a collaborator of the late W. Moffit of Harvard University. Of particular significance is the discussion of the octant rule (Moffit, Moscowitz, Woodward, Klyne and Djerassi) in Chap. 13. This generalization, which permits the prediction of the sign of the Cotton effect, has not been up till now generally available. Of the manifold uses of the octant rule, the determination of the preferred conformation of *cis*-decalones and the study of conformational mobility of monocyclic cyclohexanones is particularly interesting.

The remainder of the book describes the application of rotatory dispersion to various classes of compounds which have not yet been as extensively studied as ketones. These are: thiones, nitroalkanes, nitrites, aromatic compounds, xanthates, aminoacids, proteins and many others. In many of these classes interesting results have been already obtained.

It is abundantly clear that both the spectropolarimeter and Djerassi's excellent account of its uses will have, from now on, a permanent place in every modern organic laboratory.

K. WIESNER

Tetrahedron, 1960, Vol. 10, p. 127. Pergamon Press Ltd. Printed in Northern Ireland

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A list of some of the papers to be published in future issues

HUANG YAO-TSENG: Experiments on the synthesis of substances related to tetracyclines.

G. E. LEWIS: Structures of the mono-acid cations of 4-aminoazobenzene and its derivatives.

E. CLAR and A. MCCALLUM: The significance of benzenoid rings for the stability of aromatic hydrocarbons.

SUSUMU OHSHIRO: Studies on the syntheses of hydrogenated quinolines and isoquinolines as analgesics—XVIII. Synthesis of 3-hydroxy-N-methyl-8-aza-des-N-morphinan, (4-methyl-9-hydroxy-5·10b-trimethylene-1,2,3,4,4a,5,6,10b-octahydrobenzo [F] quinoline).

P. SENGUPTA, S. K. SENGUPTA and H. N. KHASTGIR: Terpenoids and related compounds—II. Investigations on the structure of nimbin.

C. GARDNER SWAIN and RICHARD F. W. BADER: The nature of the structure difference between light and heavy water and the origin of the solvent isotope effect—I.

C. GARDNER SWAIN, RICHARD F. W. BADER and EDWARD R. THORNTON: A theoretical interpretation in mixtures of light and heavy water—II.

J. SMITH and R. H. THOMSON: Diquinones—I. The oosporein–tomichaedin degradation.

F. KORTE und H. SEIPER: Papierchromatographische Charakterisierung von Haschisch-Inhaltsstoffen.

H. H. JAFFÉ and M. ORCHIN: Hybridization in carbon monoxide.

M. K. BHATTACHARJEE, R. B. MITRA, B. D. TILAK and M. R. VENKITESWAREN: Synthesis of heterocyclic steroids—III. An unsuccessful attempt at the synthesis of B-nor-6-thiaequilenin through 3-cyano-7-methoxy-4-oxo-1,2,3,4-tetrahydrodibenzothiophene.

G. V. BHIDE, N. L. TIKOTKAR and B. D. TILAK: Synthesis of heterocyclic steroids—IV. Synthesis of dl-B-nor-6-oxaequilenin.

C. V. BHIDE, N. L. TIKOTKAR and B. D. TILAK: Synthesis of heterocyclic steroids—V. Attempted synthesis of B-nor-6-aza-6-methyl-equilenin.

D. L. E. BRONNERT and B. C. SAUNDERS: Toxic fluorine compounds containing the C–F link—XI. Lability of the fluorine atom in 2-fluoroethanol.

P. BROWN, J. BURDON, T. J. SMITH and J. C. TATLOW: 5,5,-Trifluorolaevulic acid and some derived compounds.

P. NARASIMHA RAO and L. R. AXELROD: Synthesis of 2-hydroxyestradiol-17β.

Tetrahedron, 1960, Vol. 10, pp. 129 to 134. Pergamon Press Ltd. Printed in Northern Ireland

STRUCTURES OF THE MONO-ACID CATIONS OF 4-AMINOAZOBENZENE AND ITS DERIVATIVES

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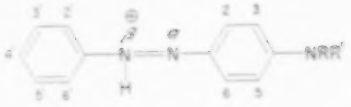
(*Received* 22 *February* 1960)

Abstract—Conflicting views exist on the structures of the mono-acid cations of 4-aminoazobenzene and its derivatives. The azonium structure (I) and the ammonium structure (II) have been separately upheld as correct, but detailed examination of spectroscopic data shows that both forms exist in solution as tautomeric equilibrium mixtures (I ⇌ II).

VARIOUS conclusions have been published concerning the structures of the mono-acid cations of 4-aminoazobenzene and its derivatives in solution. It has been generally accepted for a long time that the proton in these cations is attached to the β-azo nitrogen atom, forming the resonance-stabilized azonium ion (Ia ↔ Ib).[1–5]



Ia

Ib

II

In recent years some authors[6–9] have discredited this view and advanced arguments in favour of the ammonium structure (II).

It is clear, however, from careful examination of the ultra-violet and visible spectra in solutions of different acidities that both forms are present as a tautomeric equilibrium mixture (I ⇌ II) in nearly every case.[10–17]

[1] A. Hantzsch and F. Hilscher, *Ber. Dtsch. Chem. Ges.* **41**, 1171 (1908).
[2] F. Kehrmann, *Ber. Dtsch. Chem. Ges.* **48**, 1933 (1915).
[3] A. Hantzsch, *Ber. Dtsch. Chem. Ges.* **52**, 509 (1919).
[4] C. R. Bury, *J. Amer. Chem. Soc.* **57**, 2115 (1935).
[5] M. T. Rogers, T. W. Campbell and R. W. Maatman, *J. Amer. Chem. Soc.* **73**, 5122 (1951).
[6] H. H. Jaffé, *J. Chem. Phys.* **21**, 415 (1953).
[7] I. M. Klotz, H. A. Fiess, J. Y. Chen Ho and M. Mellody, *J. Amer. Chem. Soc.* **76**, 5136 (1954).
[8] W. S. McGuire, T. F. Izzo and S. Zuffanti, *J. Org. Chem.* **21**, 632 (1956).
[9] L. Pentimalli, *Tetrahedron* **5**, 27 (1959).
[10] A. Hantzsch and A. Burawoy, *Ber. Dtsch. Chem. Ges.* **63**, 1760 (1930).
[11] G. M. Badger, R. G. Buttery and G. E. Lewis, *J. Chem. Soc.* 1888 (1954).
[12] G. Cilento, E. C. Miller and J. A. Miller, *J. Amer. Chem. Soc.* **78**, 1718 (1956).
[13] E. Sawicki, *J. Org. Chem.* **21**, 605 (1956).
[14] E. Sawicki, *J. Org. Chem.* **22**, 365 (1957).
[15] E. Sawicki, *J. Org. Chem.* **22**, 621 (1957).
[16] E. Sawicki, *J. Org. Chem.* **22**, 1084 (1957).
[17] H. H. Jaffé and Si-Jung Yeh, *J. Org. Chem.* **22**, 1281 (1957).

In the present review an account of the main experimental data and interpretations leading to these diverse conclusions is given. A suggestion that the proton could be bonded preferentially to the α-azo nitrogen in the mono-acid cations[18] is considered too untenable from theoretical argument and spectroscopic evidence[5,11] to warrant detailed discussion.

It is obvious from electronic theory[19,20] that structures such as IIIb contribute significantly to resonance in 4-aminoazobenzene and its derivatives (IIIa↔IIIb), so that the electronic charge at the β-azo nitrogen atom must be considerably greater than at the nitrogen atoms of azobenzene. The electron density at the amino group, on the other hand, should be much lower than normal due to electron-attraction by the azo nitrogen.

IIIa

IIIb

It might be expected, therefore, that a proton should attack either the amino group or the β-azo nitrogen with more or less comparable case, but not the α-azo nitrogen.

The absorption spectra of 4-aminoazobenzene and its N,N-diethyl and N,N-dimethyl derivatives in acidic solution led Hantzsch and Burawoy[10] to propose that the mono-acid cations of these compounds exist as tautomers. Such tautomerism was confirmed by Badger *et al.*[11] after extension of spectroscopic studies to other azo-compounds. The rationale underlying the conclusions in this work is summarized as follows with reference to Table 1.

TABLE 1. ABSORPTION MAXIMA OF AZOBENZENE DERIVATIVES AND THEIR MONO-ACID CATIONS IN AQUEOUS ETHANOL

Compound	References	Free base		Mono-acid cation			
		K band		K′ band		Q band	
		λ_{max} (mμ)	ε_{max} ($\times 10^{-3}$)	λ_{max} (mμ)	ε_{max} ($\times 10^{-3}$)	λ_{max} (mμ)	ε_{max} ($\times 10^{-3}$)
Azobenzene	11	320	21	—	—	—	—
4,4′-Azoanisole	11	350	16	—	—	500	43
4-Phenylaminoazobenzene	11	420	28	—	—	540	61
4-Methylaminoazobenzene	11	410	23	320	8	510	39
4-Dimethylaminoazobenzene	10, 11	420	24	320	10	520	34
4-Ethylaminoazobenzene	11	410	24	320	13	510	29
4-Ethylmethylaminoazobenzene	11	430	25	320	15	530	22
4-Aminoazobenzene	10, 11	380	22	320	18	500	11
4-Diethylaminoazobenzene	10, 11	440	29	320	20	520	10
4-Dimethylamino-3-methylazobenzene	25	375	18	320	22	—	—
4-Dimethylamino-2-methylazobenzene	25	420	27	326	4	520	50
4-Dimethylamino-2′-methylazobenzene	25	410	27	326	16	520	10

[18] S. E. Sheppard and P. T. Newsome, *J. Amer. Chem. Soc.* **64**, 2937 (1942).
[19] B. Pullman and J. Baudet, *C. R. Acad. Sci., Paris* **238**, 2529 (1954).
[20] A. Pullman and B. Pullman, *C. R. Acad. Sci., Paris* **243**, 1322 (1956).

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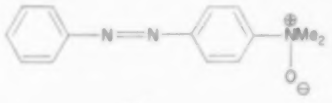
Azobenzene in aqueous ethanolic solution displays a strong absorption peak at 320 mμ. This has been assigned to a transition of the $\pi \rightarrow \pi^*$ type[21] and designated the K band.[22] The K band of 4-aminoazobenzene arises in the 380 mμ region in the same solvent. The K bands of the N-substituted compounds have their maxima at even longer wavelengths, 410–440 mμ, bathochromic displacement being a result of the conjugating power of the amino-group with the azo linkage. In solution of sufficient acidic strength to ensure in each case that the compound is present entirely as the mono-acid salt, no absorption maximum appears in the 400 mμ region. There is instead one band in the 500–540 mμ region and another at approximately 320 mμ. The intensities of the bands, designated Q and K′ bands respectively,[11] were found to vary inversely as substituents were introduced or changed.

The Q bands, being at long wavelengths, have been attributed to the azonium ions in which high degrees of resonance-stabilization are apparent (Ia $\leftrightarrow$ Ib).[1–5] On the other hand, the K′ bands are associated with the ammonium cations (II), essentially for the reason that they lie in the same region as the K band of azobenzene.

It is well known that aniline and N-substituted anilines in neutral solutions absorb at longer wavelengths and higher intensities than benzene, whereas the absorption characteristics of the anilinium ions are very similar to those of benzene.[23] If II were the structure of a 4-aminoazobenzene mono-acid cation its absorption should be similar to that of azobenzene in neutral solution. This reasoning is augmented by the following facts. 4-Dimethylaminostilbene in acidic solution has an absorption spectrum almost identical with that of stilbene in neutral solution, as expected from proton-addition to the dimethylamino group.[24] 4-Dimethylaminoazobenzene methiodide,[10] assigned the quaternary ammonium structure, and 4-phenylazodimethylaniline N-oxide (IV)[9] show very similar spectra to azobenzene.



IV

Furthermore, 4,4′-azoanisole as the free base shows a K band at 350 mμ and its mono-acid cation, presumably existing only in the azonium form, exhibits a strong Q band at 500 mμ, but no K′ band.

The inverse relationship between the intensities of the Q and K′ bands shows that the cations exist in equilibrium mixtures (I $\rightleftharpoons$ II) and the relative intensities of the peaks measure the proportions of the tautomers present.[11,12]

Effects of substitution in various positions of the aromatic nuclei of 4-dialkylaminoazobenzenes provide additional support for the tautomeric equilibrium theory and clearly indicate that the β-azo nitrogen is the atom bonding the proton in the azonium ion.

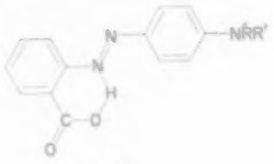
4-Dimethylamino-3-methylazobenzene[25] in acidic solution shows no absorption in the 500 mμ region, but a very intense band at 320 mμ. In this case it is obvious that the 3-methyl group prevents the dimethylamino group from assuming coplanarity

[21] P. P. Birnbaum, J. H. Linford and D. W. G. Style, *Trans. Faraday Soc.* **49**, 735 (1953).
[22] A. Burawoy, *J. Chem. Soc.* 1865 (1937).
[23] A. Wohl, *Bull. Soc. Chim.* [5], **6**, 1312 (1939).
[24] G. E. Lewis, *J. Org. Chem.* In press.
[25] J. A. Miller, R. W. Sapp and E. C. Miller, *J. Amer. Chem. Soc.* **70**, 3458 (1948).

with the aromatic nucleus, thereby restricting its mesomeric effect. Addition of the proton in these circumstances appears to occur only at the dimethylamino group. 3,5-Dimethyl-4-dimethylaminoazobenzene behaves similarly.[26]

Comparison of the spectra of the 2-methyl and 2′-methyl derivatives of 4-dimethylaminoazobenzene under acidic conditions[25] indicates that the proton does not attack the α-azo nitrogen atom. The cation of the 2-methyl compound displays an intense Q band and a weak K′ band. A strong K′ band and weak Q band are shown by the 2′-methyl compound. A methyl group substituted in the 2-position of azobenzene is known to sterically hinder reactions preferentially at the nearer azo nitrogen atom.[27,28] This accounts for restriction of proton-addition at the β-azo nitrogen in 4-dimethylamino-2′-methylazobenzene, whereas in 4-dimethylamino-2-methylazobenzene the β-azo nitrogen is not hindered and the proton attaches itself almost exclusively to this position.

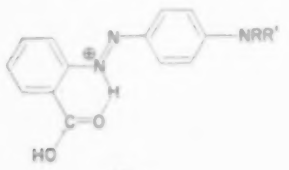
According to Ross and Warwick[29] a variety of substituents in the 2′-position of 4-dialkylaminoazobenzenes markedly oppose protonation at the azo linkage. A 2′-carboxy group, however, behaves anomalously due to strong intramolecular hydrogen



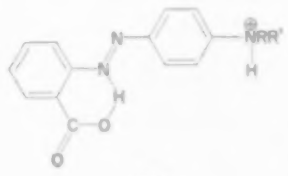
V

bonding to the β-azo nitrogen atom (V).[29,30] The hydrogen bond appears to actually aid formation of the azonium ion.

In acidic solution such derivatives display intense Q bands; a very weak K′ band is shown by the 4-dimethylamino compound (VI; R = R′ = Me) and no K′ band at all in the case of the di(2-chloroethyl)amino compound (VI; R = R′ = CH_2CH_2Cl).[29] The equilibrium (VIa ⇌ VIb) is therefore displaced almost completely to the left.



VI a



VI b

The foregoing discussion recounts the main evidence in support of the tautomeric equilibrium theory. Additional support has come from other sources.[13–17]

The arguments advanced in favour of proton-addition solely at the β-azo nitrogen or the amino nitrogen atom are not so consistently logical. In many cases the interpretations are unsound because insufficient experimental data have been considered. Those workers who have maintained that the mono-acid cations possess only the

[25] L. Horner and H. Müller, *Ber. Dtsch. Chem. Ges.* **89**, 2756 (1956).
[27] G. M. Badger and G. E. Lewis, *J. Chem. Soc.* 2147 (1953).
[28] G. M. Badger and G. E. Lewis, *J. Chem. Soc.* 2156 (1953).
[29] W. C. J. Ross and G. P. Warwick, *J. Chem. Soc.* 1719 (1956).
[30] I. N. Zhmurova, *J. Gen. Chem. U.S.S.R.* **27**, 2745 (1957).

azonium structure have failed to recognize the significance of absorption in the 320 mμ region.[5]

Exponents of the opposite view have based their conclusions on various types of experimental data. McGuire *et al.*[8] proposed, after comparing the absorption spectra of azobenzene, 4-dimethylaminoazobenzene and Methyl Orange in neutral and acidic solutions, that protonation occurs only at the dimethylamino group. It is clear, however, from the incomplete absorption curves published by these workers that the critical peaks in the 500 mμ region were ignored. Their interpretations may therefore be disregarded.

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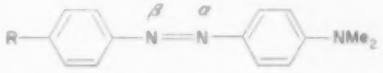
In a different approach, Jaffé[6] concluded that the Hammett reaction constants (ρ)[31] relating to the primary and secondary ionizations of 4′-substituted 4-dimethylaminoazobenzenes (VII)[5] constituted evidence for the first proton becoming attached to the dimethylamino group and the second proton to the azo-linkage. The primary and secondary reaction constants found were $\rho_1 = 0{\cdot}55$ and $\rho_2 = 4{\cdot}35$ respectively.



VII

It was assumed that the reaction constant for protonation at the β-azo nitrogen should be of comparable value to that for the dimethylamino group in *p*-substituted dimethylanilines ($\rho = 4{\cdot}19$), and hence the above conclusion was reached. This is quite dubious because it may be just as reasonably assumed that the reaction constants for the dimethylanilines and the amino group of the azo-compounds should be quantitatively similar in view of the unrestricted conjugation between the substituent and the amino group in both cases.

Klotz *et al.*[7] claim to have proved unequivocally that the first proton adds to 4-dimethylaminoazobenzene exclusively at the dimethylamino group from a comparison of the p*Ka* values for azobenzene (—2·5), 4-dimethylaminoazobenzene (3·5) and dimethylaniline (5·1) determined in aqueous media. It was estimated, on the assumption that the electronic effects of azo and nitro groups are roughly comparable, that the *p*-phenylazo group in 4-dimethylaminoazobenzene should lower the basicity of the dimethylamino group from 5·1 to approximately 3, the latter value being given as correct for *p*-nitrodimethylaniline. Using the reverse approach, these authors supposed that the electron-donating dimethylamino group in the 4-position of azobenzene might be expected to raise the p*Ka* of the azo linkage from —2·5 to 0·0. The observed value for 4-dimethylaminoazobenzene therefore led them to conclude that the mono-acid cation has the proton attached solely to the dimethylamino group.

It cannot be conceded that this is an unequivocal conclusion. In the reasoning process, whereby 4-dimethylaminoazobenzene is treated alternately as a *p*-substituted dimethylaniline and a 4-substituted azobenzene, the very nature of the resonance hybrid (IIIa ↔ IIIb) is overlooked. Furthermore, the respective p*Ka* values of 3 and 0·0 so suggested are approximations of insufficient accuracy to permit any comparison of the type attempted. No evidence was given to support the proposal that 0·0 should be the upper limit of the basicity of the azo linkage, and the value of 3 suggested as the lower limit of the basicity of the dimethylamino group appears to be too high because

[31] L. P. Hammett, *Physical Organic Chemistry* p. 186. McGraw-Hill, New York (1940).

Hall[32] estimated the p*Ka* of *p*-nitrodimethylaniline in aqueous solution to be 0·8, an appreciably lower figure than that stated.

In an attempt to reinforce their argument, Klotz *et al.* erroneously contended that absorption in the 500 mμ region could be attributed to the amonium ion (II). Their interpretations of spectra have been already criticized.[12–14,24,30]

Pentimalli[9] has stated that the formation of 4-phenylazodimethylaniline N-oxide (IV), when 4-dimethylaminoazobenzene is oxidized by perbenzoic acid, is in agreement with the conclusions reached by Klotz *et al.*[7] Attack by the peracid at the dimethylamino-nitrogen atom, however, is not necessarily an indication of highest electron-density at that position. It could well be that there is greater steric resistance to oxidation at the azo linkage. Pentimalli's absorption curve for 4-phenylazodimethylaniline N-oxide, on the other hand, is in disagreement with the spectral interpretations advanced by Klotz *et al.*

Apart from studies of the mono-acid cations in solution, the solid hydrochlorides of 4-aminoazobenzene and 1-phenylazo-4-naphthylamine have been examined by infra-red spectroscopy.[34] As the free bases, aniline, 1-naphthylamine, 4-aminoazobenzene and 1-phenylazo-4-naphthylamine have absorption bands in the 3250–3400 cm^{-1} region due to the free amino groups.[33] Aniline hydrochloride and 1-naphthylamine hydrochloride display no absorption above 3100 cm^{-1}, but 4-aminoazobenzene hydrochloride and 1-phenylazo-4-naphthylamine hydrochloride both show three bands in the 3100–3350 cm^{-1} region.[34] It is clear from these observations that the proton is not attached exclusively to the amino group in the salts of the azo-compounds.

[32] N. F. Hall, *J. Amer. Chem. Soc.* **52,** 5115 (1930).
[33] G. D. Bagratishvili, *Dokl. Akad. Nauk SSSR* **96,** 753 (1954).
[34] G. D. Bagratishvili, *Soobshcheniya Akad. Nauk Gruzin. SSR* **17,** 615 (1957).

Tetrahedron, 1960, Vol. 10, pp. 135 to 143. Pergamon Press Ltd. Printed in Northern Ireland

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FUNGUS PIGMENTS—XII*

THE STRUCTURE AND SYNTHESIS OF THELEPHORIC ACID

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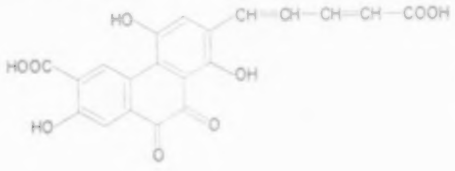
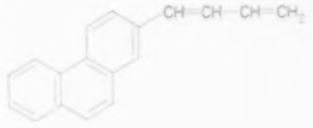
(*Received* 21 *March* 1960)

Abstract—Degradative and spectroscopical evidence, as well as biogenetic considerations led to the conclusion that thelephoric acid is 2,3,8,9-tetrahydroxybenzobis[1,2-b,4,5-b']benzofuran-6,12-quinone(VI). This view was confirmed by synthesis, involving condensation of chloranil with two molecules of 3,4-dimethoxyphenol and subsequent demethylation.

THELEPHORIC acid was investigated by Kögl *et al.*[1] and on the basis of degradation reactions formula I was proposed. Doubt concerning this formula was cast by Millward and Whiting,[2] who synthesized 1,2'-phenanthryl-1,3-butadiene(II), which Kögl *et al.*[7] claimed to have obtained from thelephoric acid acetate and record properties very different from those reported by Kögl *et al.*[1] As no authentic sample was available for direct comparison, the possibility of polymorphism and/or stereoisomerism could not be ignored, but the necessity of a more thorough study of thelephoric acid was obvious.



I



II

Thelephoric acid, first found in several species of *Thelephora*[1,3] also occurs in *Hydnum* spp.[4–7] For the present work the sporophores of *Hydnum suaveolens* collected in 1948 were used.†

Extraction of the fungus material with acetone gave thelephoric acid in a yield of about 0·6 per cent. Thelephoric acid is best recrystallized from pyridine, but the solvent can only be completely removed by prolonged heating under vacuum to 120–150°. Thelephoric acid dissolves quite readily in dimethyl sulphoxide and crystallizes upon addition of ethanol but again the dimethyl sulphoxide is very difficult to remove completely.

Thelephoric acid has an absorption maximum at 493 mμ in pyridine.[1] In alcohol

* Part XI: *Acta Chem. Scand.* **13**, 1305 (1959). A preliminary account of the present work has appeared in *Suomen Kemistilehti* **B 33**, 72 (1960).

† This material was generously placed at the author's disposal by Prof. H. Erdtman, Stockholm.

[1] F. Kögl, H. Erxleben and L. Jänecke, *Liebigs Ann.* **482**, 105 (1930).
[2] B. B. Millward and M. C. Whiting, *J. Chem. Soc.* 903 (1958).
[3] W. Zopf, *Bot. Z.* 69 (1889).
[4] J. Zellner, *Monatsh.* **36**, 615 (1915).
[5] M. Sawada, *Nippon Ringaku Kaishi* **34**, 110 (1952); *Chem. Abstr.* **47**, 4436 (1953).
[6] M. Sawada, *Nippon Ringaku Kaishi* **40**, 195 (1958); *Chem. Abstr.* **52**, 18638 (1958).
[7] J. Gripenberg, *Acta Chem. Scand.* **12**, 1411 (1958).

this maximum is shifted to 480 mμ (the complete spectrum in alcohol is reproduced in Fig. 1). In acetone the maximum is at 463 mμ and in dioxan at 450 mμ. In alkaline solution thelephoric acid has a weak maximum at 720–730 mμ.

In the I.R. spectrum (in KBr-disk the position of the carbonyl band varies in different preparations between 1635 and 1660 cm^{-1}. Read and Vining[8] report 1629 cm^{-1} for this band, which is regarded as that of a quinone carbonyl. Even in the region 1400–1100 cm^{-1} some differences can be observed. On the other hand the finger print region is very consistent

The analytical figures of Kögl *et al.*[1] favoured the composition $C_{20}H_{12}O_9$, but fit

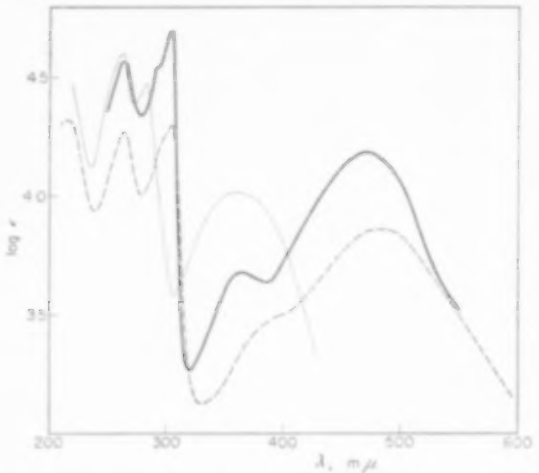


FIG. 1. Spectra of: (– – – –) thelephoric acid(VI) (ethanol); (———) thelephoric acid tetramethyl ether(VIII) (chloroform) and (. . . . .) thelephoric acid tetra-acetate(IX) (dioxan).

equally well $C_{18}H_{10}O_8$.[9] The difficulty in removing solvent of crystallization makes the analytical results somewhat uncertain, but on an extensively dried sample figures point to $C_{18}H_8O_8$ as the correct composition.

Potentiometric titration in dimethyl sulphoxide with tetrabutylammonium hydroxide gave an equivalent weight of 176, corresponding to two ionizable hydrogens. Comparison of the titration curves with other strongly acidic phenols show thelephoric acid as a slightly weaker acid than *o*-nitrophenol.

Acetylation gave the known[1] acetate originally regarded as a triacetate, but acetyl values (33·8%) are higher than those reported earlier[1] (25·24 and 24·97%) and the analyses agree well with a tetra-acetate ($C_{26}H_{16}O_{12}$). The U.V. spectrum (Fig. 1) shows a pronounced hypsochromic shift relative to thelephoric acid. In the I.R. spectrum the band at 1780 cm^{-1} is attributed to the ester carbonyls and the band at 1680 cm^{-1} to the quinone carbonyl.

Reductive acetylation gave the leuco-acetate,[1] which is now regarded as dihydro-thelephoric acid hexa-acetate ($C_{30}H_{22}O_{14}$). The U.V. spectrum (Fig. 2) has also been reported by Read and Vining,[8] and in agreement with these authors is the presence of a single strong band in the carbonyl region of the I.R. spectrum at 1760 cm^{-1}, due to ester carbonyls.

[8] G. Read and L. C. Vining, *Canad. J. Chem.* **37**, 1442 (1959).
[9] J. Gripenberg, *Svensk Kem. Tidskr.* **72**, 256 (1960).

The U.V. spectrum of the leuco-acetate cannot be that of a leuco-acetate of I, which should be similar to that of II.[2] Also the lack of any absorption in the I.R. spectrum, that could be attributed to the carboxyl groups in the leuco-acetate of I clearly shows that this formula cannot be correct.[9]

As can be seen from Fig. 2 the spectrum of thelephoric acid leuco-acetate is

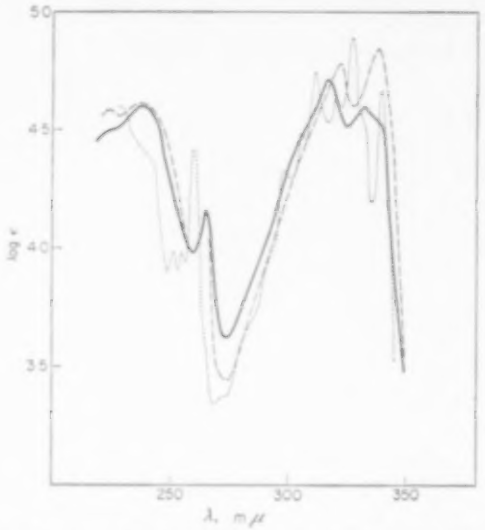


FIG. 2. Spectra of: (———) dihydrothelephoric acid hexa-acetate(XI) (dioxan), (– – – –) dihydroisothelephoric acid hexa-acetate (dioxan) and (.....) benzobis [1,2-b,4,5-b′] benzofuran(III) (cyclohexane).

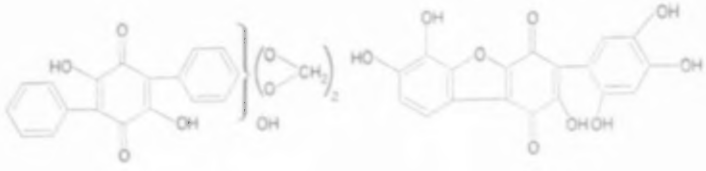
similar to that of benzobis[1,2-b,4,5-b′]benzofuran(III), and on the basis of the analytical evidence should be a hexa-acetoxy derivative. This has also been suggested by Read and Vining[8] based on a comparison of the spectrum of thelephoric acid leuco-acetate with the less similar spectrum of 2,11-diacetoxybenzobis[1,2-b,4,3-b′]-benzofuran.

III

Further proof of the presence of the benzobis[1,2-b,4,5-b′]benzofuran ring system in thelephoric acid was obtained from zinc dust distillation of thelephoric acid acetate. Kögl *et al.*[1] obtained in this reaction what they believed to be 1,2′-phenanthryl-1,3-butadiene(II), but the crystalline sublimate described by Kögl *et al.* proved to be a mixture of at least five components. By a combination of chromatography and recrystallization one component was isolated in a pure state and identified as *p*-terphenyl. A second component is most probably biphenyl, although it was not obtained pure. Three further components were characterized only by their U.V. spectra, and one had maxima at exactly the same positions, and with the same relative intensities as benzobis[1,2-b,4,5-b]benzofuran(III), whose presence in the mixture is thus strongly indicated.

Aghoramurthy *et al.*[10] have also reported the formation of *p*-terphenyl from the zinc dust distillation of thelephoric acid acetate, but their conclusion that thelephoric acid is a simple 2,5-diphenyl-*p*-benzoquinone derivative, such as IV cannot, however, be correct.

It has been shown[11] that 2,5-diphenyl-*p*-benzoquinones with hydroxyl or methoxyl groups in the *p*-positions of the aromatic rings have a long-wave maximum at 380–405 mμ. This should not be changed by the introduction of more hydroxyl groups and a compound of structure IV should therefore be expected to absorb in the same region or only at a slightly longer wave-length, whereas thelephoric acid, absorbs at 450 mμ in dioxan, the same solvent in which the other measurements were made. The U.V. spectrum of thelephoric acid leuco-acetate differs completely from the spectrum one would expect for the leuco-acetate of a compound with structure IV. This should be similar to the spectrum of 2',5'-diacetoxy-4,4''-dimethoxy-*p*-terphenyl (see experimental, with a maximum at 280–290 mμ, and not above 300 mμ. As we have been unable to get a positive test[12] for a methylenedioxy group in thelephoric acid or any of its derivatives, it is possible that the Indian workers had a different substance.*



IV V

On the assumption that thelephoric acid leuco-acetate is a hexa-acetoxybenzobis-[1,2-b,4,5-b']benzofuran thelephoric acid may be formulated as a tetrahydroxy-benzobis[1,2-b,4,5-b']benzofuranquinone.

Read and Vining[8], proposed formula V for thelephoric acid, assuming that ring closure to the benzobis[1,2-b,4,5-b']benzofuran system occurred on acetylation and reductive acetylation. Formula V does not agree with analytical figures now reported, and cannot explain that thelephoric acid acetate and leuco-acetate are readily hydrolysed to thelephoric acid (in the case of the leuco-acetate the primarily formed dihydro-thelephoric acid is spontaneously oxidized in air to thelephoric acid). The opening of only one furan ring under the conditions of the hydrolysis is extremely improbable.

Further evidence against formula V is obtained from the methylation of thelephoric acid. The product corresponds to a tetramethyl ether of thelephoric acid, the U.V. spectrum (Fig. 1) indicating that no fundamental change in the chromophore had taken place during methylation. A compound with structure V should give a hexa-methyl ether, or possibly an anhydrotetramethylether, with the spectrum very different from that of thelephoric acid.

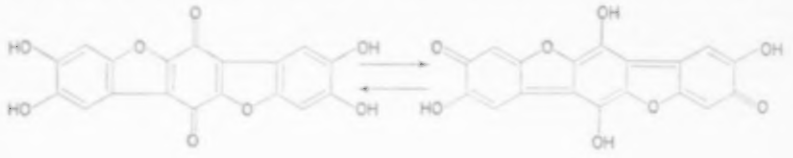
The position of the quinone group in the benzobis[1,2-b,4,5-b']benzofuran ring system, cannot be in one of the terminal aromatic rings, as *p*-terphenyl is formed during zinc dust distillation. The other end of the molecule should contain a preformed

* See "Note added in proof", p. 143.

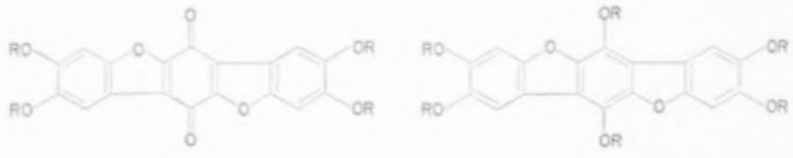
[10] K. Aghoramurthy, K. G. Sarma and T. R. Seshadri, *Tetrahedron Letters* No. 8, 20 (1959).
[11] J. Gripenberg, *Acta Chem. Scand.* **12**, 1762 (1958).
[12] O. A. Stamm, H. Schmid and J. Büchi, *Helv. Chim. Acta* **41**, 2006 (1958).

dibenzofuran ring system which should not loose its oxygen in the zinc dust distillation.[13,14] If the quinone group is in the central ring or extended over the whole ring system the oxygen bridges would terminate in a quinone double bond and the removal of these oxygen atoms appears more likely. Such a loss of an oxygen between an aromatic ring and a quinonoid system was observed in the zinc dust distillation of cinnabarin.[15]

The positions of the four hydroxyl groups could not be established analytically. Formula VI which is closely related to the structure of other fungus pigments of the diphenyl-*p*-benzoquinone type, is likely on biogenetic considerations and was established by synthesis. Acharya *et al.*[16] synthesized 3,9-dimethoxybenzobis-



VI VII



VIII, R=CH_3 X, R=CH_3

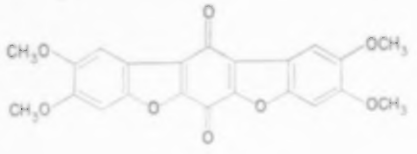
IX, R=CH_3CO XI, R=CH_3CO

[1,2-b,4,5-b′]benzofuran-6,12-quinone by condensation of chloranil with two molecules of 3-methoxyphenol. By substituting 3,4-dimethoxyphenol for 3-methoxyphenol 2,3,8,9-tetramethoxybenzobis[1,2-b,4,5-b′]benzofuran-6,12-quinone(VIII) should be formed. The reaction, gave a very difficultly soluble compound, whose U.V. and I.R. spectra were completely identical with those of thelephoric acid tetramethyl ether. Demethylation gave thelephoric acid, identified by its I.R. spectrum.

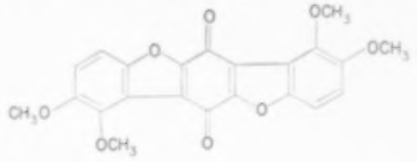
This synthesis of thelephoric acid does not, constitute unequivocal proof of the structure of thelephoric acid. The condensation of chloranil with 3,4-dimethoxyphenol could also lead to 2,3,9,10-tetramethoxybenzobis[1,2-b,5,4-b′]benzofuran-6,12-quinone(XII). Acharya *et al.*[16] have, however, shown that the analogous condensation of chloranil with *β*-naphthol proceeds through 2,5-dichloro-3,6-di-*β*-naphthoxy-*p*-benzoquinone and it is therefore reasonable to assume that in the present case the reaction cannot give XII. Furthermore XII is a derivative of *m*-terphenyl, whereas thelephoric acid is definitely a derivative of *p*-terphenyl. That the condensation should occur in the 2-position of the 3,4-dimethoxyphenol giving 1,2,7,8-tetramethoxybenzobis[1,2-b,4,5-b′]benzofuran-6,12-quinone(XIII) is highly unlikely in view of

[13] W. Hoffmeister, *Leibigs Ann.* **159**, 191 (1871).
[14] H. Erdtman and N. E. Stjernström, *Acta Chem. Scand.* **13**, 653 (1959).
[15] J. Gripenberg, E. Honkanen and O. Patoharju, *Acta Chem. Scand.* **11**, 1485 (1957).
[16] R. V. Acharya, B. D. Tilak and M. R. Venkiteswaran, *J. Sci. Ind. Res. India* **16B**, 400 (1957).

the demonstrated unreactivity of this position in ethers of hydroxyhydroquinone.[17] Thelephoric acid tetramethyl ether must therefore have structure VIII and thelephoric acid on this basis is either VI or its tautomere VII. The similarity of the U.V. spectra of thelephoric acid and its methyl ether clearly indicate that they have the same



XII



XIII

chromophore. A compound with structure VII would be expected to have a different spectrum and VI must be the correct structure of thelephoric acid.

The resonance stabilization of the anion common to VI and VII explains the relatively strong acidity of thelephoric acid. That thelephoric acid absorbs at longer wavelengths than similarily substituted diphenyl-*p*-benzoquinones is certainly due to the fact that the benzene rings in thelephoric acid are forced into the same plane as the quinone ring.

Two further reactions of thelephoric acid are of interest.

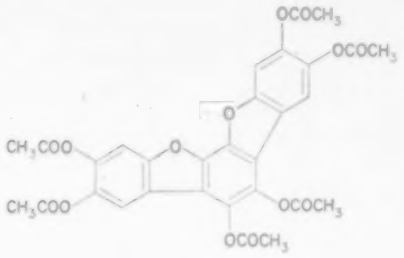
When the methylation of thelephoric acid was carried out for a longer period with excess of dimethyl sulphate, the initially formed difficultly soluble tetramethyl ether dissolved and a colourless compound was obtained in good yield. This had a higher methoxyl-content, showed no carbonyl band in the I.R. spectrum and when heated with hydrobromic acid gave thelephoric acid. It was thought to be formed by methylation of an enolic form of thelephoric acid and therefore called isothelephoric acid hexamethyl ether[9] but later was proved identical with dihydrothelephoric acid hexamethyl ether(X), described earlier by Kögl *et al.*[1] and Aghoramurthy *et al.*[10] The reducing agent in the reaction was found to be pyridine present when the thelephoric acid had not been thoroughly dried after recrystallization.

Decker[18] has shown that methylpyridinium hydroxide is oxidized to N-methyl-α-pyridone by potassium ferricyanide and although no report has been found that quinones can effect this reaction, it is believed that the reaction is analogous to the Decker-oxidation, the quinone being reduced to the hydroquinone, which is instantly methylated. Preliminary experiments with other quinones have shown that they also can be reductively methylated in the presence of pyridine and a more thorough study of this reaction is in hand.

On the assumption that thelephoric acid was enolizable the preparation of the enol acetate by boiling with acetic anhydride and sodium acetate was attempted. This reaction gave a colourless compound termed isothelephoric acid acetate.[9] Both the U.V. (Fig. 2) and I.R. spectra are similar to those of thelephoric acid leuco-acetate, but definitely not identical. The compound is readily hydrolysed but no pure product has as yet been obtained. It is isomeric with thelephoric acid leuco-acetate and it is thought that some kind of rearrangement as well as reduction has taken place during the acetylation. The compound is, therefore, called dihydroiso-thelephoric acid hexa-acetate. One possible structure would be XIV. A reduction

[17] W. Baker and C Evans, *J. Chem. Soc.* 372 (1938).
[18] H. Decker, *J. Prakt. Chem.* [2] **47**, 28 (1893).

of a quinone to the corresponding hydroquinone acetate under the conditions used is known, *p* benzoquinone can be converted in low yield to hydroquinone diacetate



XIV

upon boiling with acetic anhydride and sodium acetate.[19,20] The formation of this compound and its structure will be the subject of further work.

EXPERIMENTAL

Analyses were by Dr. A. Bernhardt, Mülheim, Germany. The I.R. spectra were measured as KBr-disks with a Beckman IR-5 instrument and the U.V. spectra with a Beckman DK-2 instrument.

Isolation of thelephoric acid

The finely powdered fungus material (750 g) was extracted in a Soxhlet-apparatus with acetone. The almost black precipitate formed was thoroughly washed with water and the insoluble residue recrystallized from pyridine, giving very dark violet crystals (8 g). This material still containing pyridine on heating at 140°/0·1 mm lost 41% of its weight, corresponding to a total yield of pure solvent-free thelephoric acid of 4·7 g. (Found: C, 60·79, 61·42; H, 2·30, 2·41. $C_{15}H_8O_8$ requires: C, 61·37; H, 2·29%). U.V. spectra: (ethanol) λ_{max} 217 (log ε 4·33), 264 (log ε 4·27), 305 (log ε 4·30), 390 (infl) (log ε 3·48) and 483 mμ (log ε 3·86), λ_{min} 241 (log ε 3·94), 280 (log ε 4·01) and 330 mμ (log ε 3·13). Owing to the very low solubility of thelephoric acid in ethanol these extinction values are probably too low; (pyridine) λ_{max} 311 (log ε 4·51), 395 (infl) (log ε 3·59) and 493 mμ (log ε 4·05), λ_{min} 340 mμ (log ε 3·11); (dioxan) λ_{max} 450 mμ; (acetone) λ_{max} 463 mμ. Main I.R. maxima: 3550 (m), 3260 (s), 1645 (s), 1610 (m), 1530 (s), 1480 (m), 1430 (w), 1385 (m), 1365 (m), 1332 (w), 1267 (s), 1175 (s), 1128 (m), 1085 (m), 1038 (s), 863 (m), 840 (w), 798 (s), 749 (w), 713 (w) and 698 (w) cm^{-1}.

Thelephoric acid tetra-acetate(IX). This was obtained as described by Kögl *et al.*[1] m.p. 330–335°. (Found: C, 59·79; H, 3·36; CH_3CO, 33·8, $C_{26}H_{16}O_{12}$ requires: C, 60·01; H, 3·10; $(CH_3CO)_4$, 33·1%). U.V. spectrum: (dioxan) λ_{max} 263 (log ε 4·60), 283 (log ε 4·47) and 360 mμ (log ε 4·01), λ_{min} 236 (log ε 4·12), 273 (log ε 4·39) and 307 mμ (log ε 3·59). Main I.R. maxima: 1780 (s), 1680 (s) 1625 (w), 1585 (w), 1535 (s), 1478 (m), 1448 (m), 1370 (s), 1318 (m), 1262 (s), 1205 (vs), 1159 (s), 1125 (s), 1076 (m), 1033 (vs), 1015 (m), 919 (m), 907 (m), 882 (m), 832 (m), 807 (m), 753 (w), 728 (w) and 709 (w) cm^{-1}.

Thelephoric acid leuco-acetate(XI). This was prepared according to Kögl *et al.*[1] m.p. 380–390°. (Found: C, 58·69; H, 3·57; CH_3CO, 41·3, $C_{30}H_{22}O_{14}$ requires: C, 59·41; H, 3·66; $(CH_3CO)_6$, 42·5%). Main I.R. maxima: 1760 (s), 1635 (w), 1600 (w), 1538 (m), 1462 (s), 1428 (m), 1412 (m), 1377 (s), 1347 (m), 1320 (m), 1292 (m), 1263 (m), 1205 (vs), 1161 (s), 1130 (s), 1074 (s), 1023 (s), 991 (m), 920 (m), 879 (m), 802 (m), 742 (w), 727 (w), 706 (w), 674 (w) and 658 (w) cm^{-1}.

Methylation of thelephoric acid

(a) Thelephoric acid (air dried material, 150 mg) was methylated with dimethyl sulphate (2 g) and potassium carbonate (2 g) in acetone by boiling on a water bath for 3 hr. The insoluble residue was washed with water, dilute sodium hydroxide, acetone and ether leaving a dark violet crystalline

[19] E. Sarauw, *Liebigs Ann.* **209**, 93 (1881).
[20] K. Buschka, *Ber. Dtsch. Chem. Ges.* **14**, 1326 (1881).

mass (95 mg). This was recrystallized from anisol giving *thelephoric acid tetramethyl ether*(VIII) as brown-violet crystals, which decompose without melting at 360°. (Found: C, 64·25; H, 3·99; OCH_3, 26·5. $C_{22}H_{16}O_8$ requires: C, 64·70; H, 3·95; $(OCH_3)_4$, 30·4%). U.V. spectrum: (chloroform) λ_{max} 264 (log ε 4·57), 293 (infl) (log ε 4·54), 303 (log ε 4·70), 364 (log ε 3·68) and 472 mμ (log ε 4·18), λ_{min} 280 (log ε 4·34), 320 (log ε 3·27) and 386 mμ (log ε 3·64). Main I.R. maxima: 1661 (s), 1618 (w), 1588 (w), 1528 (s), 1500 (m), 1481 (s), 1460 (m), 1435 (s), 1378 (w), 1363 (w), 1325 (m), 1253 (s), 1217 (s), 1194 (w), 1186 (w), 1148 (m), 1092 (s), 1040 (s), 1000 (m), 858 (m), 846 (m), 783 (s), 765 (w), 751 (w), 723 (w), 711 (w) and 700 (w) cm^{-1}.

(b) Thelephoric acid (air dried material, 150 mg) was methylated as described under (a) except that the reaction time was 40 hr. The insoluble part was treated as above giving thelephoric acid tetramethyl ether (13 mg). The dark green acetone solution was evaporated to dryness under vacuum and the residue treated with water yielding a yellow crystalline precipitate. This was recrystallized from chloroform/alcohol giving colourless crystals of dihydrothelephoric acid hexamethyl ether (X, 85 mg), m.p. 260–261°. (Found: C, 66·04; H, 5·11; OCH_3, 41·2. $C_{24}H_{22}O_8$ requires: C, 65·74; H, 5·06; $(OCH_3)_6$, 42·4%). U.V. spectrum: (dioxan) λ_{max} 228 (log ε 4·64), 252 (log ε 4·55), 275 (log ε 4·11), 306 (infl) (log ε 4·40), 318 (log ε 4·66), 341 (log ε 4·57) and 357 mμ (log ε 4·81), λ_{min} 240 (log ε 4·51), 270 (log ε 4·08), 284 (log ε 3·86), 331 (log ε 4·30) and 346 mμ (log ε 4·51). Main I.R. maxima: 1631 (w), 1605 (w), 1536 (s), 1483 (s), 1463 (s), 1441 (s), 1385 (s), 1343 (w), 1300 (s), 1270 (s), 1238 (m), 1212 (s), 1191 (s), 1184 (s), 1148 (s), 1085 (m), 1060 (s), 1038 (m), 1004 (m), 913 (w), 858 (m), 808 (m), 781 (m), 753 (m), 688 (w) and 664 (w) cm^{-1}. This compound was identical with one prepared from thelephoric acid according to Kögl *et al.*[1], for which they report m.p. 246°. Aghoramurthy *et al.*[10] report m.p. 254–256°. The identification was based on a mixed m.p. and on completely superimposable I.R. spectra.

(c) Thelephoric acid (dried over phosphorus pentoxide under vacuum, 100 mg) was methylated as described under (b). The insoluble portion gave thelephoric acid tetramethyl ether (95 mg), and no crystalline material could be obtained from the almost colourless filtrate.

Reductive methylation of thelephoric acid tetramethyl ether. Thelephoric acid tetramethyl ether (50 mg) was methylated with dimethylsulphate (2 g) and potassium carbonate (2 g) in boiling acetone containing 0·1 ml pyridine for 20 hr. The solution gave as described for the methylation of thelephoric acid, under (b), dihydrothelephoric acid hexamethyl ether (40 mg).

Demethylation of dihydrothelephoric acid hexamethyl ether. Dihydrothelephoric acid hexamethyl ether (20 mg) was boiled with a mixture of acetic acid and hydrobromic acid. The solution gradually turned almost black with formation of a dark precipitate. This (10 mg) was recrystallized from pyridine and identified by I.R. spectrum as thelephoric acid.

Zinc dust distillation of thelephoric acid. The reaction was carried out as described by Kögl *et al.*[1] The light petroleum solution of the crystalline sublimate was chromatographed on a column of alumina, and the chromatogram eluted with the same solvent. The chromatogram was inspected in ultra-violet light which revealed several fluorescent zones and treated as separate fractions. The first fraction with only a very weak fluorescence gave a few crystals m.p. 65-70° and a single maximum in the U.V. spectrum at 247 mμ (cyclohexane). This substance is very probably biphenyl.

The second fraction with a strong blue fluorescence contained the bulk of the material. Recrystallization of the residue gave colourless crystals with m.p. 209–210°, λ_{max} (cyclohexane) 274 mμ. The compound was identified as *p*-terphenyl by its I.R. spectrum. The mother liquor from the crystallization of *p*-terphenyl contained a substance with λ_{max} 264 and 296 mμ which has not been obtained completely free from *p*-terphenyl and has not yet been identified.

The third fraction had a whitish blue fluorescence and contained only a very small amount of material whose U.V. spectrum had maxima at 260, 298, 305, 311, 320, 327 and 339 mμ. These maxima coincide exactly with those of benzobis[1,2-b,4,5-b′]benzofuran. The rather high absorption between 265 and 280 mμ indicates that some *p*-terphenyl is still present in this fraction.

The fourth fraction which did not clearly separate from the preceding fraction showed in the U.V. spectrum in addition to the maxima of benzobis[1,2-b,4,5-b′]benzofuran two strong maxima at 288 and 302 mμ.

2,3,8,9-*Tetramethoxybenzobis*[1,2-b, 4,5-b′]*benzofuran*-6,12-*quinone*(VIII). Sodium (0·45 g) was dissolved in abs alcohol (15 ml) and 3,4-dimethoxyphenol[21] (3 g) added. This solution was added to a suspension of chloranil (2·4 g) in abs alcohol (40 ml) and the mixture boiled for 10 min. Abs alcohol

[21] R. I. Meltzer and J. Doczi, *J. Amer. Chem. Soc.* **72**, 4986 (1950).

(15 ml) in which sodium (0·45 g) had been dissolved was then added and the boiling continued for 45 min. After cooling the precipitate was thoroughly washed first with alcohol and then with water. The remaining crude product (1·0 g) was once extracted with boiling anisol and the insoluble residue extracted with chloroform in a Soxhlet. 2,3,8,9-Tetramethoxybenzobis[1,2-b,4,5-b′]benzofuran-6,12-quinone precipitated from the solution as brown violet crystals (700 mg). A sample for analysis was recrystallized from bromocymene (Found: C, 64·25; H, 3·95. $C_{22}H_{16}O_8$ requires: C, 64·70; H, 3·95%). The U.V. and I.R. spectra were identical with those of thelephoric acid tetramethylether.

2,3,7,8-*Tetrahydroxybenzobis*[1,2-b,4,5-b′]*benzofuran*-6,12-*quinone* (VI). 2,3,8,9-Tetramethoxybenzobis[1,2-b,4,5-b′]benzofuran-6,12-quinone (40 mg) and pyridine hydrochloride (4 g) were heated in an oil bath at 205–210° for ½ hr resulting in a clear dark melt. After cooling this was treated with water and the blue precipitate recrystallized from pyridine giving dark violet crystals (15 mg) after drying over phosphorus pentoxide under vacuum. The U.V. and I.R. spectra were identical with those of thelephoric acid.

Dihydroisothelephoric acid hexa-acetate. Thelephoric acid (100 mg) was boiled with acetic anhydride and anhydrous sodium acetate for 16 hr. A clear light brown solution resulted. The precipitate, formed upon cooling was recrystallized from acetic acid, giving colourless needles (130 mg), which decomposed at 300°. (Found: C, 59·70; H, 3·72; CH_3CO, 41·4. $C_{30}H_{22}O_{14}$ requires: C, 59·41; H, 3·66; $(CH_3CO)_6$, 42·5%). U.V. spectrum: (dioxan) λ_{max} 224 (log ε 4·58), 237 (log ε 4·62), 265 (log ε 4·17), 321 (log ε 4·78) and 338 mμ (log ε 4·84), λ_{min} 228 (log ε 4·56), 260 (log ε 3·97), 274 (log ε 3·44) and 328 mμ (log ε 4·59). Main I.R. maxima: 1780 (s), 1748 (s), 1631 (w), 1534 (w), 1462 (s), 1433 (w), 1408 (w), 1372 (s), 1338 (w), 1321 (m), 1280 (w), 1261 (m), 1197 (vs), 1157 (s), 1129 (s), 1082 (m), 1012 (m), 986 (w), 951 (w), 943 (m), 872 (m), 854 (w), 818 (w), 803 (w), 777 (w), 728 (w), 709 (w), 683 (w), 671 (w) and 657 (w) cm^{-1}.

2′,5′-*Diacetoxy*-4,4″-*dimethoxy*-p-*terphenyl*. 2,5-bis(*p*-methoxyphenyl)-*p*-benzoquinone[22] was heated to boiling with acetic anhydride, zinc dust and a drop of pyridine. The hot yellow solution was filtered and the filtrate treated with water. The colourless precipitate was recrystallized from dioxan, m.p. 204–205°. (Found: C, 71·07; H, 5·47. $C_{24}H_{22}O_6$ requires: C, 70·92; H, 5·46%). U.V. spectrum: (ethanol) λ_{max} 276 mμ (log ε 4·50), λ_{min} 241 mμ (log ε 3·90).

Acknowledgements—The author wishes to express his gratitude to Prof. H. Erdtman, Stockholm, for donating the fungus material and to Prof. H. Erdtman and Mr. N. E. Stjernström, Fil. lic., for supplying benzobis[1,2-b,4,5-b′]benzofuran and several of its derivatives. The author's thanks are also due to Mr. C. Enebäck, Techn. lic., of this department for the potentiometric titrations.

Note added in proof. An exchange of samples with the Indian workers has now been arranged and comparisons carried out in both laboratories have established the identity of the preparations.

[22] R. Pummerer and E. Prell, *Ber. Dtsch. Chem. Ges.* **55**, 3105 (1922).

Tetrahedron, 1960, Vol. 10, pp. 144 to 147. Pergamon Press Ltd. Printed in Northern Ireland

SYNTHESIS OF 2-HYDROXYESTRADIOL-17β[1]

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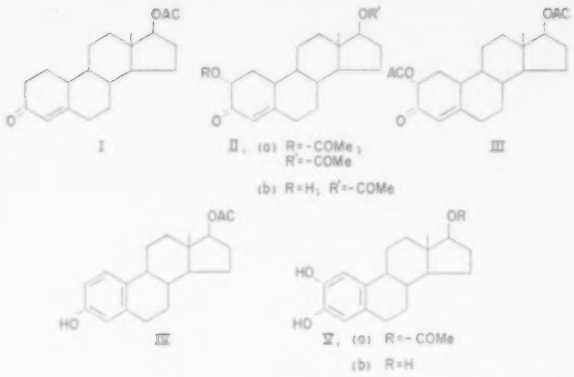
Abstract—The synthesis of 2-hydroxyestradiol-17β from 19-nortestosterone is described.

RECENTLY, two new metabolites of estrogens, 2-methoxy estrone,[2,3] and 2-methoxy-estriol[4] have been isolated from human urine. To explain the formation of these new metabolites a two step mechanism was proposed[2] involving the oxidation of estrogens at C-2 position leading to 2-hydroxyestrogens and subsequent methylation giving rise to 2-methoxy estrogens. For a better understanding of the mechanism it was found necessary to synthesize 2-hydroxy-estrogens and the synthesis of 2-hydroxyestradiol-17β forms the subject of this paper. It may be mentioned in this connexion that the synthesis of 2-hydroxyestradiol has been outlined by a different method[5] without any physical constants for the intermediates or the final compound, and no further detailed publication to this date is available.

17β-Acetoxy-4-estrene-3-one[6] (19-nortestosterone 17β-acetate) (I) was reacted with lead tetra-acetate[7] to give a mixture of two isomeric diacetates in about 20–25 per cent yield from which 2α,17β-diacetoxy-4-estrene-3-one(IIa) m.p. 235–237°, and 2β,17β-diacetoxy-4-estrene-3-one(III) m.p. 185–186° were separated by fractional crystallization; of the two diacetates, compound IIa, m.p. 235–237°, predominated the mixture. The structural proof and configurations assigned to these two diacetates followed from their elemental analysis, and a comparison of their molecular rotations. The molecular rotatory difference (ΔM_D) for the introduction of acetoxy group in IIa is −48·5 whereas in III ΔM_D is −522·8. It was shown previously[7d,8] that the 2β-acetoxy group contributes more strongly to the levorotation in Δ^4-3-keto steroids.

When it was attempted to isomerize III to the more stable form IIb by refluxing

[1] Preliminary communication, *Chem. & Ind.* 1454 (1959).
This work was supported in part by a Grant No. 1078 from National Institute of Health, Division of Arthritis and Metabolic Diseases, and a Grant from the Wyeth Institute for Medical Research.
[2] S. Kraychy and T. F. Gallagher, *J. Biol. Chem.* **299**, 519 (1957).
[3] L. L. Engel, B. Baggett and P. Carter, *Endocrinology* **61**, 112 (1957).
[4] J. Fishman and T. F. Gallagher, *Arch. Biochem. Biophys.* **77**, 511 (1958).
[5] G. C. Mueller, *Nature, Lond.* **176**, 127 (1955).
[6] J. A. Hartman, A. J. Tomasewski and A. S. Dreiding, *J. Amer. Chem. Soc.* **78**, 5662 (1956).
[7] [a] G. Ehrhart, H. Ruschig and W. Amuller, *Angew. Chem.* **52**, 363 (1939); [b] T. Reichstein and C. Montigel, *Helv. Chim. Acta* **22**, 1212 (1939); [c] E. Seebeck and T. Reichstein, *Helv. Chim. Acta* **27**, 948 (1944); [d] F. Sondheimer, S. Kaufmann, J. Romo, H. Martinez and G. Rosenkranz, *J. Amer. Chem. Soc.* **72**, 4712 (1953); [e] G. Rosenkranz, O. Mancera and F. Sondheimer, *J. Amer. Chem. Soc.* **77**, 145 (1955); [f] R. L. Clarke, K. Dobriner, A. Mooradian and C. M. Martini, *J. Amer. Chem. Soc.* **77**, 661 (1955).
[8] P. Narasimha Rao and L. R. Axelrod, *J. Amer. Chem. Soc.* In press.



I II, (a) R=-COMe; R'=-COMe
(b) R=H, R'=-COMe
III IV V, (a) R=-COMe
(b) R=H

with potassium acetate in glacial acetic acid,[7f] the acetoxy group in III was eliminated, and estradiol 17β-acetate(IV) was obtained by aromatization of ring A.

Controlled hydrolysis of IIa, under a nitrogen atmosphere and at room temperature with exactly one equivalent of potassium hydroxide selectively hydrolysed the C-2 acetate group to give 2α-hydroxy-17β-acetoxy-4-estrene-3-one(IIb). The hydroxyl group in IIb was then oxidized with bismuth trioxide in acetic acid[9] to give the 2,3-dione which immediately aromatized and 2,3-dihydroxy-17β-acetoxyestra 1,3,5(10)-triene(Va) resulted. However, compound Va could be obtained from the mixture of diacetates IIa and III by selective hydrolysis of C-2 acetate group with one equivalent of potassium hydroxide to a mixture of 2α and 2β-hydroxy compounds and then oxidizing the mixture with bismuth trioxide in acetic acid. The 17β-acetoxy compound Va was then hydrolyzed by stirring at room temperature with 1N sodium hydroxide in aqueous ethanol for 18 hours to give 2,3,17β-trihydroxyestra-1,3,5 (10)-triene (2-hydroxy-estradiol-17β (Vb) in excellent yield.

Attempts to oxidize Vb using mild oxidation procedures, in the hope of obtaining 2-hydroxyestrone were not successful.

EXPERIMENTAL[10]

Melting points. All melting points were determined on samples dried under high vacuum at 60° for 24 hr and were uncorrected.

Absorption spectra. The ultraviolet absorption spectra were determined in methanol with a Cary recording spectrophotometer (Model 11 MS). The infrared absorption spectra were determined in potassium bromide disk on a Perkin–Elmer (Model 21) spectrometer.

17β-*Acetoxy-4-estrene-3-one*(19-*nortestosterone* 17β-*acetate*)(I).[11] This compound was prepared as described in the literature.[6]

Reaction of 17β-*acetoxy-4-estrene-3-one with lead tetra-acetate*

Preparation of (IIa) *and* (III). To a solution of 50 g 17β-acetoxy-4-estrene-3-one in 280 ml glacial acetic acid, 85 g lead tetra-acetate in 560 ml glacial acetic acid was added in one lot and the contents stirred at 85–90°. At the end of 2 hr, (starch–iodide test negative) the acetic acid was removed under vacuum and 4 l. ice cold water added. The residue was dissolved in 250 ml methanol and kept overnight at 10°. The mixture of diacetates (IIa) and (III) (14 g; 24%) m.p. 180–200° fractionally crystallized from methanol as 6·7g 2α,17β-*diacetoxy-4-estrene-3-one*(IIa) m.p. 235–237°, $(\alpha)_D^{23\cdot5}$ +24° ($CHCl_3$), M_D +89·9; λ_{max}^{MeOH} 240 mμ, (ε, 14,230); ν_{max}^{KBr} 1732, 1680 and 1614 cm^{-1}. (Found: C, 70·8; H, 8·1. $C_{22}H_{30}O_5$ requires: C, 70·5; H, 8·1%).

[9] W. Rigby, *J. Chem. Soc.* 793, (1951); [5] J. S. Baran, *J. Amer. Chem. Soc.* **80**, 1687 (1958).
[10] Analysis were performed by Micro-Tech Laboratories, Skokie, Illinois.
[11] Obtained from Arapahoe Chemicals Inc., Boulder, Colorado.

Isolation of (III). The mother combined liquors from the fractional crystallization were evaporated and the residue crystallized from ethyl acetate. After 3 crystallizations 1·3 g analytically pure 2*β*,17*β*-*diacetoxy*-4-*estrene*-3-*one*, (III) m.p. 185–186°, $(\alpha)_D^{23\cdot4}$ −101·6° ($CHCl_3$); M_D −380·5; λ_{max}^{MeOH} 242 mμ (ε, 16,530); ν_{max}^{KBr} 1737, 1727, 1682, and 1624 cm^{-1} was obtained. (Found: C, 70·6; H, 7·9. $C_{23}H_{30}O_4$ requires: C, 70·5; H, 8·1%).

Reaction of III *with potassium acetate in glacial acetic acid.* To a solution of 775 mg 2*β*,17*β*-diacetoxy-4-estrene-3-one(III) in 25 ml glacial acetic acid, 4 g anhydrous potassium acetate was added and refluxed in an atmosphere of nitrogen for 15 hr. The ethyl acetate extract was washed with water, 10% aqueous sodium bicarbonate, and again with water until neutral. The product (520 mg) crystallized from methanol as 3-hydroxy-17*β*-acetoxyestra-1,3,5 (10)-triene(IV) (estradiol 17*β*-monoacetate) m.p. 217–218°; $(\alpha)_D^{24}$ +40° λ_{max}^{MeOH} 280 mμ (ε, 2754), λ_{min}^{MeOH} 250 mμ, (ε, 1096), ν_{max}^{KBr} 3475, 1703, 1620, 1585 cm^{-1}; previously reported[12] m.p. 217–219°; $(\alpha)_D^{25}$ +47°; λ_{max} 280 mμ (log ε 3·42), λ_{min} 250 mμ (log ε 3·03). Acetylation of IV with pyridine and acetic anhydride gave 3,17*β*-diacetoxy-estra-1,3,5 (10)-triene (estradiol 3,17*β*-diacetate) m.p. 128–129° and its identity has been established by comparison of the infrared spectrum and mixture m.p. determination with an authentic sample.

2*α*-*Hydroxy*-17*β*-*acetoxy*-4-*estrene*-3-*one*(IIb). Compound IIa 5·78 g in 185 ml absolute methanol were stirred in an atmosphere of nitrogen at 30°. Compound IIa was not completely soluble, and 13·27 ml 0·99 M potassium hydroxide in absolute methanol was added and the stirring continued. The solution gradually turned yellow and after 13 min all solid had dissolved; 180 ml methanol containing 5 ml water was added and the stirring continued for 2 min. It was then acidified with 25 ml 1 N acetic acid and the solvent removed under vacuum at room temp and diluted with water. The product (4·8 g) crystallized from dilute methanol as 3·9 g (77% yield) 2*α*-*hydroxy*-17*β*-*acetoxy*-4-*estrene*-3-*one*(IIb) m.p. 148–149°. The analytical product m.p. 150–151°, $(\alpha)_D^{22\cdot5}$ +76·4 ($CHCl_3$) λ_{max}^{MeOH} 239·5 mμ (ε, 15,920) ν_{max}^{KBr} 3470, 1738, 1673 and 1610 cm^{-1} (Found: C, 72·4; H, 8·4. $C_{20}H_{28}O_4$ requires: C, 72·3; H, 8·5%).

2,3-*Dihydroxy*-17*β*-*acetoxyestra*-1,3,5 (10)-triene (Va). To a solution of 590 mg 2*α*-hydroxy-17*β*-acetoxy-4-estrene-3-one in 9 ml glacial acetic acid, 600 mg bismuth trioxide was added and the mixture heated at 100–105° with stirring. After 30 min another 200 mg bismuth trioxide was added and heating continued for 30 min. The ethyl acetate extract was washed with water, saturated sodium bicarbonate solution, and then with water until neutral and dried over sodium sulphate. The product crystallized from benzene to give 340 mg (58% yield) 2,3-*dihydroxy*-17*β*-*acetoxyestra*-1,3,5 (10)-*triene* (Va), m.p. 180–182°. The analytical product m.p. 183–185°; $(\alpha)_D^{22\cdot5}$ +60·3° ($CHCl_3$); λ_{max}^{MeOH} 288 mμ (ε, 4213); λ_{min}^{MeOH} 253 mμ (ε, 413); ν_{max}^{KBr} 3432, 1700, 1600, 1512 and 1446 cm^{-1} (Found: C, 72·75; H, 7·95. $C_{20}H_{28}O_4$ requires: C, 72·7; H, 7·9%).

Preparation of Va *from the mixture of diacetates* IIa *and* III. To a suspension of 12·3 g of mixture of diacetates IIa and III (m.p. 180–200°) in 600 ml absolute methanol, 28·2 ml 0·99 M potassium hydroxide in absolute methanol was added under nitrogen atmosphere and the contents stirred at 30° until all the solid was in solution. It was then diluted with 175 ml methanol containing 5 ml water, stirring continued for 6 min and then acidified with 50 ml 1N acetic acid, most of the solvent was removed under vacuum at room temp and then diluted with water. The crude mixture of 2*α* and 2*β*-hydroxy-17*β*-acetoxy-4-estrene-3-one, 10·2 g was oxidized with bismuth trioxide.

Bismuth trioxide oxidation. The aforementioned solid 10·2 was dissolved in 160 ml glacial acetic acid and 10 g bismuth trioxide added and was heated at 100–105° with stirring for 30 min; another 4 g bismuth trioxide was introduced and the heating and stirring continued for 30 min. The ethyl acetate extract was washed successively with water, saturated sodium bicarbonate solution and again with water until neutral, and dried over sodium sulphate. The product crystallized from benzene as 5·4 g (54%) of 2,3-dihydroxy-17*β*-acetoxyestra-1,3,5 (10)-triene (Va) m.p. 180–182° identical in all respects with the material obtained by bismuth trioxide oxidation of IIb.

2,3,17*β*-*Trihydroxyestra*-1,3,5 (10)-*triene* (2-*hydroxyestradiol*-17*β*) (Vb). To a solution of 1·2 g Va in 20 ml ethyl alcohol under nitrogen atmosphere, a solution of 1 g sodium hydroxide in 5 ml water was added and the mixture stirred for 18 hr at room temp, then acidified with acetic acid, diluted with water and extracted with ethyl acetate. The ethyl acetate extract was washed with water, 10% aqueous sodium bicarbonate, and again with water, and dried over sodium sulphate. The product 1·1 g crystallized from dilute methanol as 2,3,17*β*-*trihydroxyestra*-1,3,5 (10)-*triene* (2-*hydroxyestradiol*-17*β*) Vb in light tan colored prisms. The analytical product was obtained with one molecule of solvent of

[12] C. Djerassi, G. Rosenkranz, J. Romo, S. Kaufman and J. Pataki, *J. Amer. Chem. Soc.* **72**, 4534 (1950).

crystallization, m.p. 162–163° (at 102–106° the compound shrinks with loss of solvent of crystallization and melts at 162–163° with slight decomposition), $(\alpha)_D^{23.5}$ +83·2° (ethanol), λ_{max}^{MeOH} 288 mμ (ε, 4042), λ_{min}^{MeOH} 253 mμ (ε, 457); ν_{max}^{KBr} 3440 (broad band) 1600, 1512 and 1445 cm^{-1} (Found: C, 71·2; H, 8·8. $C_{18}H_{24}O_2$, CH_3OH requires: C, 71·2; H, 8·8%). The *triacetate* of Vb was prepared with pyridine and acetic anhydride in the cold, and it crystallized from methanol in colorless plates m.p. 168–169°; $(\alpha)_D^{23.5}$ +52·3 ($CHCl_3$); λ_{max}^{MeOH} 277 mμ (ε, 1480), 271 mμ (ε, 1480), λ_{min}^{MeOH} 375 mμ (ε, 1344); 248 mμ (ε, 366); ν_{max}^{KBr} 1775, 1722, 1500, 1250 and 1215 (broad) cm^{-1} (Found: C, 69·47; H, 7·37. $C_{24}H_{30}O_6$ requires: C, 69·55; H, 7·29%).

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Tetrahedron, 1960, Vol. 10, pp. 148 to 152. Pergamon Press Ltd. Printed in Northern Ireland

DIQUINONES—I

THE OOSPOREIN–TOMICHAEDIN DEGRADATION

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(*Received* 26 *March* 1960)

Abstract—It is established, by synthesis, that tomichaedin, the degradation product obtained from the dibenzoquinone, oosporein, by fusion with potash, has the structure 3-hydroxy-2-methyl-1,4-naphthaquinone-6-carboxylic acid. A mechanism for the reaction is proposed which accounts for all the products which have been isolated.

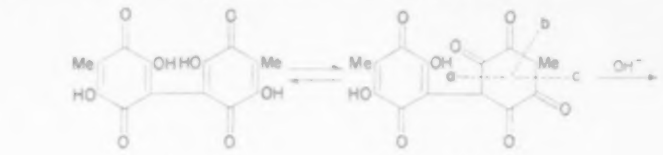
Iso-oosporein is identical with oosporein.

THE diquinone oosporein(I) has been encountered more frequently than most fungal quinones. Originally isolated from laboratory cultures of *Oospora colorans* van Beyma by Kögl and van Wessem[1], it was later obtained from *Chaetomium aureum* Chivers[2] (and other unidentified *Chaetomium* spp.)[3,4] *Verticillium psalliotae* Treschow,[5] the culture filtrate of a sterile mycelium,[4] and very recently, from an *Acremonium* sp.[6] The pigment chaetomidin, which Nishikawa[3] obtained from a *Chaetomidium* (= *Chaetomium*) sp. proved[7] to be identical with oosporein, and we have now shown that iso-oosporein,[8] the metabolic product of another unidentified mould, is also identical with oosporein. An isomeric structure was proposed by Shigematsu[8] as his material, and its derivatives, appeared to differ in several respects from oosporein, but the faults must be attributed to errors in the original work.[1] (At the time Shigematsu[9] was unaware of the later paper by Robertson *et al.*[2]) That oosporein and iso-oosporein are one and the same compound is now established by their infra-red spectra, which are identical having bands (KBr disk) at 3·03, 6·16, 7·24, 7·51, 7·71, 8·05, 9·35, 10·13, 10·48, 10·87, 13·06, 13·50, and 14·01μ.

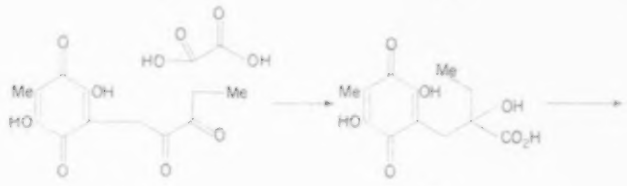
Benzoquinones are reactive compounds and greater reactivity would be anticipated for dibenzoquinones, especially when the quinone rings are close enough to allow interaction. It has already been shown[10] that internuclear reactions can take place under acid conditions, with surprising results, and in the case of oosporein a remarkable transformation occurs under alkaline conditions. In their examination of the structure of oosporein, both Nishikawa[3] and Shigematsu[8] subjected it to fusion with potassium hydroxide and so obtained a yellow compound, tomichaedin, $C_{12}H_8O_5$, which gave a red solution in alkali. On zinc-dust distillation it yielded naphthalene, and from the

[1] F. Kögl and G. C. van Wessem, *Rec. Trav. Chim.* **63**, 5 (1944).
[2] G. Lloyd, A. Robertson, G. B. Sankey and W. B. Whalley, *J. Chem. Soc.* 2163 (1955).
[3] H. Nishikawa, *J. Fac. Agric. Tottori Univ.* **1**, 71 (1952).
[4] T. Rosett, Thesis, London University (1955).
[5] H. W. Reading, Thesis, London University (1955).
[6] P. V. Divekar, R. H. Haskins and L. C. Vining, *Canad. J. Chem.* **37**, 2097 1959).
[7] M. Itahashi, Y. Murakami and H. Nishikawa, *Tohoku J. Agric. Res.* **5**, 281 (1955).
[8] N. Shigematsu, *J. Inst. Polytechnics, Osaka City Univ.* Ser. C. **5**, 100 (1956).
[9] N. Shigematsu, personal communication.
[10] H. Erdtman, *Proc. Roy. Soc.* A **143**, 223 (1934); T. Posternak, *Helv. Chim. Acta* **39**, 1564 (1956).

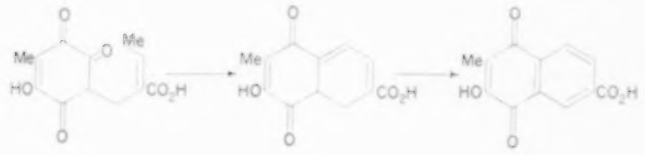
formation of numerous derivatives[3,7] it appeared to be a hydroxynaphthaquinone-carboxylic acid. The presence of a methyl group was inferred from the analyses, and its location in the quinone ring adjacent to the hydroxyl group was indicated by the negative Kesting[11] tests given by tomichaedin and its derivatives, and by the formation of trimellitic acid on oxidation of tomichaedin with alkaline permanganate[7] or hydrogen peroxide.[8] The Japanese authors were thus driven to the conclusion that tomichaedin is 3-hydroxy-2-methylnaphthaquinone-6-or-7-carboxylic acid.



I Ia



II III



IV V VI

To account for the formation of such a compound we have suggested, in a preliminary communication,[12] the following mechanism, which leads to structure VI for tomichaedin. Structure Ia is a tetraketo tautomer of oosporein;* β-keto fission of bonds *a* and *b* would lead to the formation of the α-diketone II, and so to the intermediate III by a benzilic acid transformation. Dehydration of III would be expected under the reaction conditions, and if this produced the substituted crotonic acid IV (written in a tautomeric keto form), the bicyclic structure V could then be formed by aldol condensation. The final dehydrogenation to the naphthaquinone VI is probably effected by aerial oxidation as Shigematsu found that tomichaedin is not produced when oosporein is fused with potash in an atmosphere of hydrogen. In view of the many possible reactions, the low yields (10–15%) are not surprising. If the diketone II is an intermediate then oxalic acid should be formed simultaneously, and this was in fact obtained by Nishikawa[3], but the origin of n-butyric acid, which Shigematsu isolated as its *p*-bromophenacyl ester, is less obvious. We have confirmed the formation of n-butyric acid and shown, by paper chromatography, that the volatile acids produced in the fusion reaction comprise n-butyric, propionic and acetic acids (in

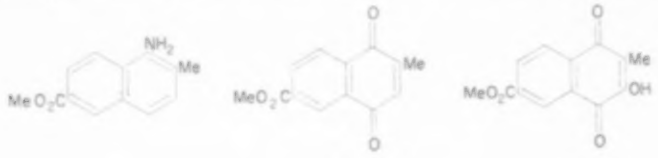
* This is written for convenience. Under the reaction conditions oosporein would be converted initially into its mesomeric anion.

[11] W. Kesting, *Ber. Dtsch. Chem. Ges.* **62**, 1422 (1929).

[12] J. Smith and R. H. Thomson, *Proc. Chem. Soc.* 95 (1959).

order of increasing concentration). If the initial degradation proceeds by fission of bonds *a* and *c* in Ia, it would give rise to α-oxobutyric acid; the same compound could also be formed from III by a reversed aldol condensation. It has not been possible to detect this product in the reaction mixture, but we have shown, in separate experiments, that on fusion with potassium hydroxide α-oxobutyric acid is destroyed and yields a mixture of n-butyric, propionic and acetic acids (in order of increasing concentration).

The structure of tomichaedin has been established by synthesis. 6-Methyl-5-nitro-2-naphthoic acid, derived from 2,6-dimethylnaphthalene,[13,14] was esterified and then reduced to the amine VII. This was coupled in aqueous acetone with diazotized aniline-2,5-disulphonic acid, and the resulting azo dye was reduced to the *p*-diamine



VII VIII IX

from which the quinone VIII was obtained by oxidation with ferric chloride. Conversion to the epoxide and hydrolysis with cold sulphuric acid then gave the hydroxyquinone IX (tomichaedin methyl ester), whence hydrolysis with hot acid gave 3-hydroxy-2-methyl-1,4-naphthaquinone-6-carboxylic acid, identical with tomichaedin.

EXPERIMENTAL

6-Methoxycarbonyl-2-methyl-1-nitronaphthalene

A mixture of 6-methyl-5-nitro-2-naphthoic acid[13,14] (2·25 g), anhydrous potassium carbonate (24 g), and dimethyl sulphate (11·5 ml) was boiled in acetone (70 ml) for 1½ hr. The product, obtained on dilution, crystallized from methanol in straw-coloured needles, m.p. 140–141°; yield 2·35 g. (Found: C, 63·4; H, 4·5; N, 5·7. $C_{13}H_{11}O_4N$ requires: C, 63·7; H, 4·5; N, 5·7%).

6-Methoxycarbonyl-2-methyl-1-naphthylamine (VII)

6-Methoxycarbonyl-2-methyl-1-nitronaphthalene (4 g) in AnalaR ethyl acetate (100 ml) was hydrogenated over Adams' catalyst (200 mg) until 3 moles of hydrogen were absorbed. The catalyst was separated by filtration and the solvent removed under reduced pressure. The *amino-ester* crystallized from methanol in yellow micro needles, m.p. 143°; yield 2·56 g. (Found: C, 72·3; H, 6·0; N, 6·4. $C_{13}H_{13}O_2N$ requires: C, 72·5; H, 6·1; N, 6·5%).

The *acetyl derivative* crystallized from methanol in white needles, m.p. 216–217°. (Found: C, 69·8; H, 5·9; N, 5·3. $C_{15}H_{15}O_3N$ requires: C, 70·0; H, 5·9; N, 5·4%).

6-Methoxycarbonyl-2-methyl-1,4-naphthaquinone (VIII)

Aniline-2,5-disulphonic acid (5.2 g; 58·5% aqueous paste) in water (35 ml) containing sodium carbonate (0·63 g) was diazotized by the addition of conc HCl (1·7 ml) and a solution of sodium nitrite (0·8 g) in water (3·5 ml). An equal volume of acetone was added to the cold diazo mixture which was then stirred mechanically and treated dropwise (30 min) with a solution of 6-methoxycarbonyl-2-methyl-1-naphthylamine (2·3 g) in acetone (40 ml). After being stirred for 2–3 hr in the ice-bath and then for a further 2 hr at room temp, the mixture was set aside overnight. The bluish-red azo dye was collected, washed, and dried, and then crushed and suspended in hot water (85 ml). After addition of conc HCl (22·5 ml) the mixture was heated to 60° on a steam-bath and treated

[13] F. Mayer and E. Alken, *Ber. Dtsch. Chem. Ges.* **55**, 2278 (1922).
[14] C. C. Price, *J. Amer. Chem. Soc.* **62**, 2245 (1940).

gradually with zinc dust (11·5 g). Reduction was complete in 30 min. Residual zinc was removed by filtration and washed well with hot water. To the combined filtrate and washings (at 60°) there was added a filtered solution of anhydrous ferric chloride (8·4 g) in water (16·8 ml) containing conc HCl (1·4 ml). The solution immediately became green and the *quinone* which separated was collected, on cooling, and crystallized from methanol (charcoal) in pale-yellow needles, m.p. 157–158°; yield 1·24 g. (Found: C, 67·9; H, 4·4. $C_{13}H_{10}O_4$ requires: C, 67·8; H, 4·4%).

The *leuco-diacetate* formed long white needles (from light petroleum, b.p. 100–120°), m.p. 162°. (Found: C, 64·6; H, 5·1. $C_{17}H_{16}O_6$ requires: C, 64·55; H, 5·1%).

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6-Methoxycarbonyl-2-methyl-1,4-naphthaquinone-2,3-epoxide

A hot solution of 6-methoxycarbonyl-2-methyl-1,4-naphthaquinone (0·62 g) in methanol (70 ml) was cooled to 45° and treated with hydrogen peroxide (1·3 ml; 30%) and a solution of sodium carbonate (0·25 g) in water (6·4 ml). The mixture was stirred at 45° for 5 min, diluted with water (300 ml), and cooled overnight on ice. The *epoxide* which separated, crystallized from aqueous methanol (charcoal) in cream-coloured needles, m.p. 136°; yield 0·40 g. (Found: C, 63·2; H, 4·1. $C_{13}H_{10}O_5$ requires: C, 63·4; H, 4·1%).

3-Hydroxy-6-methoxycarbonyl-2-methyl-1,4-naphthaquinone (IX)

6-Methoxycarbonyl-2-methyl-1,4-naphthaquinone-2,3-epoxide (0·42 g) was dissolved in ice-cold conc H_2SO_4 (4·5 ml) and, after 15 min at 0°, the solution was diluted with water (17 ml). The precipitated *hydroxyquinone* formed deep-yellow crystals, m.p. 213°, when crystallized from benzene–light petroleum (b.p. 100–120°); yield 0·29 g. (Found: C, 63·2; H, 4·0. $C_{13}H_{10}O_5$ requires: C, 63·4; H, 4·1%). The *acetate* crystallized from methanol in yellow plates, m.p. 144–145°. (Found: C, 62·2; H, 4·1. $C_{15}H_{12}O_6$ requires: C, 62·5; H, 4·2%).

3-Hydroxy-2-methyl-1,4-naphthaquinone-6-carboxylic acid (VI)

(a) A solution of the hydroxyquinone-ester (0·27 g) in conc H_2SO_4 (2·7 ml) was diluted with water (5·4 ml) and glacial acetic acid (2·7 ml) and boiled under reflux for 1 hr. On cooling, the solution was poured into water and the solid which separated was crystallized from methanol forming thin yellow needles, m.p. and mixed m.p. with tomichaedin, 282–283° (decomp) [lit[3,8] 284° (decomp); 279–280°]; yield 0·16 g. (Found: C, 62·2; H, 3·4. $C_{12}H_8O_5$ requires: C, 62·1; H, 3·5%). The infra-red and ultra-violet spectra of the natural and synthetic products were identical. Principal bands: (KBr disk) 3·1, 5·805, 5·97, 6·09, 6·23, 6·91, 7·18, 7·33, 7·59, 7·84, 8·28, 9·27, 12·70, 12·90, 13·63, 14·34, 14·86, 15·41 μ; λ max 260, 335, 382 mμ (log ε 4·41, 3·49, 3·24 respectively) λ inf 283 mμ (log ε 4·13) in ethanol; λ max 240, 286, 488 mμ (log ε 4·40, 4·38, 3·50 respectively) λ inf 345 mμ (log ε 3·13) in ethanolic $KHCO_3$.

(b) A solution of 6-methoxycarbonyl-2-methyl-1,4-naphthaquinone-2,3-epoxide (0·5 g) in conc H_2SO_4 (5 ml) was diluted with water (10 ml) and glacial acetic acid (5 ml) and boiled under reflux for 1 hr. The product (0·26 g) obtained on dilution of the solution was identical with that obtained in (a).

The quinone formed an acetate which crystallized from methanol in yellow prisms, m.p. 205° (lit[3,8] 205°). (Found: C, 61·1; H, 3·7. Calc. for $C_{14}H_{10}O_6$: C, 61·3; H, 3·7%).

Fusion of oosporein with potassium hydroxide

Oosporein (0·5 g) was fused with potassium hydroxide (5 g) in the way described by Nishikawa[3]. By acidification of the potassium salt which separated there was obtained a small amount of material which crystallized from methanol in yellow needles, m.p. 282° (decomp) (3–4 mg). The ultra-violet absorption of this product was the same as that of authentic tomichaedin. Acidification of the fusion liquor produced a strong smell of fatty acids and caused the separation of more yellowish-brown material. The mixture was steam-distilled and the distillate (A) made immediately alkaline to phenol red with aqueous barium hydroxide. The barium salts were converted to the ammonium salts for chromatography. The liquor which remained after steam-distillation was saturated with sodium chloride and extracted with ether. The material (B) obtained in this way was then examined chromatographically.

Chromatography

The volatile acids were identified by the method of Duncan and Porteous[15]. Four components were detected in (A). One component did not move from its starting position; the others corresponded in position to samples of acetic, propionic, and n-butyric acids co-chromatographed with the unknown mixture. The relative concentrations of the acids were acetic $\gg$ propionic $>$ n-butyric. The non-volatile material (B) contained several components and the best results were obtained by using the irrigants[16] (1) n-butanol/water/formic acid (10:4:3) or (2) s-butanol saturated with water/propionic acid (95:5). Four non-acidic components were detected on the unsprayed chromatograms. [R_f values in irrigant (2) were 0·84 (pink), 0·74, 0·53, 0·40 (all yellowish-brown)]. Two acidic components were detected when the chromatograms were sprayed with bromophenol blue[17] or similar indicators. One corresponded to oxalic acid but the other [R_f 0·65 in irrigant (2)] was not identified. No trace of an α-keto-acid could be found in either (A) or (B) although chromatograms of both fractions were treated with sprays specific for the detection of α-keto-acids.[18]

A sample of α-oxobutyric acid was fused with potassium hydroxide (same conditions as for oosporein). The fractions obtained by steam-distillation of the acidified mixture were examined chromatographically as before. The distillate was found to contain acetic, propionic and n-butyric acids and another component having R_f 0·0. No trace of α-oxo butyric acid was found, and examination of the residual liquor showed that the keto-acid had been completely destroyed.

Acknowledgements—One of us (J. S.) is grateful to the Executive Committee of the Shirley Institute for the award of a Fellowship. We are indebted to Dr. H. Nishikawa for a specimen of tomichaedin, to Drs. N. Shigematsu and W. B. Whalley for samples of oosporein, and to Dr. V. C. Farmer for the infra-red spectra.

[15] R. E. B. Duncan and J. W. Porteous, *Analyst* **78**, 641 (1953).
[16] *Modern Methods of Plant Analysis* Vol. II, pp. 545 and 573. Springer-Verlag, Berlin (1955).
[17] A. R. Jones, E. J. Dowling and W. J. Skraba, *Analyt. Chem.* **25**, 395 (1953).
[18] Ref. 16, p. 552.

Tetrahedron, 1960, Vol. 10, pp. 153 to 159. Pergamon Press Ltd. Printed in Northern Ireland

PAPIERCHROMATOGRAPHISCHE CHARAKTERISIERUNG VON HASCHISCH-INHALTSSTOFFEN

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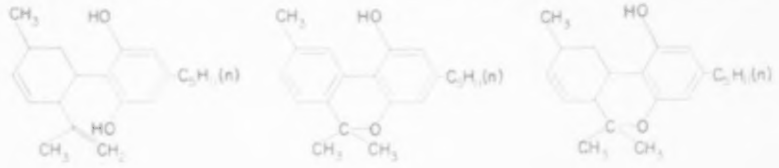
(*Received* 25 *March* 1960)

Abstract—The hashish-components cannabidiol, cannabinol and tetrahydrocannabinol have been separated by chromatography using paper impregnated with silicon resin. The spots can be identified by combined application of spray reagents. This new method allows an exact identification of the euphorically active cyclic ether "tetrahydrocannabinol" and appears to be suitable to replace physiological tests.

Zusammenfassung—Die Haschisch-Inhaltsstoffe Cannabidiol, Cannabinol und Tetrahydrocannabinol lassen sich durch Chromatographie an einem mit Silikonharz imprägnierten Papier voneinander trennen. Eine Identifizierung der Flecke ist durch kombinierte Anwendung von Sprühreagentien möglich. Das entwickelte Verfahren gestattet auch den sicheren Nachweis des euphorisch wirkenden Tetrahydrocannabinols und scheint daher geeignet, physiologische Tests zu ersetzen.

AUF Grund zahlreicher Untersuchungen von Wood *et al.*[1] konnte die Struktur der Haschisch-Inhaltsstoffe Cannabidiol(I), Cannabinol(II) und Tetrahydrocannabinol(III)



I II III

aufgeklärt werden. Ihre Isolierung geschieht durch Destillation oder durch Gegenstromverteilung[2] von Cannabisextrakten.

Die euphorische Wirkung des Haschisch beruht auf seinem Gehalt an Tetrahydrocannabinol, während Cannabidiol und Cannabinol unwirksam sind.[3] Die Prüfung der Haschischaktivität erfolgte bisher entweder nach dem Gayertest oder dem Ataxiatest.[4] Wegen der Unzuverlässigkeit dieser physiologischen Tests[5] war es von

[1] T. B. Wood, W. T. N. Spivey und T. H. Easterfield, *J. Chem. Soc.* **69**, 539 (1896); **75**, 20 (1899); F. Bergel, *Liebigs Ann.* **482**, 55 (1930); F. Bergel und K. Vögele, *Ibid.* **493**, 250 (1932); R. S. Cahn, *J. Chem. Soc.* 986 (1930); 630 (1931); 1342 (1932); 1400 (1933). Zusammenfassende Übersicht über die Literatur bis 1938, die sich mit den Inhaltsstoffen von Cannabis sativa beschäftigt, bei A. H. Blatt, *J. Wash. Acad. Sci.* **28**, 465 (1938); C. I, 967 (1939); R. Adams, M. Harfenist und S. Loewe, *J. Amer. Chem. Soc.* **71**, 1624 (1949), und vorhergehende Mitt. von R. Adams und Mitarbeitern.—T. S. Work, F. Bergel und A. R. Todd, *Biochem J.* **33**, 123 (1939)—F. Bergel, A. L. Morrison, H. Rinderknecht, A. R. Todd, A. D. Macdonald und G. Woolfe, *J. Chem. Soc.* 286 (1943), und vorhergehende Mitt. von A. R. Todd und Mitarbeitern.

[2] F. Korte und H. Sieper, *Liebigs Ann.* **630**, 71 (1960).

[3] R. Adams, M. Hunt und J. H. Clark, *J. Amer. Chem. Soc.* **62**, 196 (1940).

[4] R. Adams, S. Loewe, Ch. Jelinek und H. Wolff, *J. Amer. Chem. Soc.* **63**, 1971 (1941); R. Gosh, A. R. Todd und D. C. Wright, *J. Chem. Soc.* 137 (1941).

[5] P. B. Russell, A. R. Todd, S. Wilkinson, A. D. Macdonald und G. Woolfe, *J. Chem. Soc.* 169 (1941); R. Adams, S. Loewe, Ch. Jelinek und H. Wolff, *J. Amer. Chem. Soc.* **63**, 1971 (1941).

Interesse, eine gut reproduzierbare und einfache Methode zum Nachweis von Cannabinolverbindungen, besonders des aktiven Tetrahydrocannabinols, zu finden. Dazu schien die Papierchromatographie geeignet.

Die bisher in der Literatur beschriebenen Verfahren der Papierchromotographie von Cannabinolverbindungen sind unbefriedigend. Duquenois[6] chromatographierte Cannabisextrakte mit einem Aceton-Ammoniak-Gemisch und erhielt bei einem R_F-Wert von 0,4 einen unter der Analysenquarzlampe blau fluoreszierenden, mit dem Reagens nach Beam[7] blau anfärbbaren Fleck. Der Nachweis ist nach eigenen Untersuchungen unspezifisch, da eine Trennung nicht erfolgt und die Beam-Reaktion nur auf Cannabidiol anspricht.[2]

Wir chromatographierten Gemische von I, II und III absteigend mit Methanol an 2043 a (Schleicher u. Schüll) und erhielten bei einem R_F-Wert von 0,80 mit Paulys Reagens[8] für alle Cannabinolverbindungen ockerbraune Flecke[2]. Eine Trennung erfolgte jedoch auch nicht.

Weitere Versuche, Cannabinolgemische an unbehandeltem Papier aufzutrennen, verliefen sowohl mit neutralen wie mit sauren Lösungsmittelsystemen negativ. Wegen des stark hydrophoben Charakters der Substanzen findet offensichtlich eine Verteilung zwischen der mobilen organischen Phase und dem Cellulose-Wasser-Komplex des Papiers nicht mehr statt.

Geringe Trenneffekte wurden an acetylierten Papieren[9] mit über 20 prozentigen Acetylgehalten beobachtet, die Flecken liessen sich jedoch nur schwer oder überhaupt nicht mit den unten beschriebenen Reagentien anfärben.

Erfolgreich dagegen verliefen die Versuche mit dem Spezialpapier 2043 a hy (Schleicher u. Schüll), einem mit einer 5 prozentigen Lösung eines Silikonharzes (Dowex 1107) in Cyclohexan getränkten Linterspapier.

Bei der Wahl des Lösungsmittelsystems liessen sich die Erfahrungen verwerten, die bei der Auftrennung von Cannabinolverbindungen durch Craig-Verteilung von Cannabisextrakten gemacht wurden.[2] Die hierbei bewährten Lösungsmittelsysteme waren auch für die Papierchromatographie brauchbar. Die besten Ergebnisse wurden mit dem Zweiphasensystem Ligroin/Benzol/Chloroform/Methanol/Wasser = 2:2:1:4:1 erzielt. Die Chromatographie erfolgt absteigend mit der wässrigen Phase. Man erhält grössere, aber scharf umgrenzte Flecke mit genügend unterschiedlichen R_F-Werten. In Abb. 1 ist ein Chromatogramm der reinen und im Gemisch aufgetragenen Cannabinolverbindungen dargestellt.

Das Chromatogramm lässt erkennen:

(1) Getrennt chromatographiert zeigen die Cannabinole höhere R_F-Werte als im Substanzgemisch (siehe 1–3 gegenüber 4).

(2) Die R_F-Werte der aus den Pflanzenextrakten abgetrennten Cannabinole sind mit denen eines rein synthetischen Cannabinolgemisches identisch (siehe 4 gegenüber 5 und 6).

(3) Cannabidiol, Cannabinol und Tetrahydrocannabinol geben Flecke von unterschiedlicher Gestalt. Diese ist unabhängig von der Konzentration und der Art und Menge der Begleitsubstanzen und kann daher zur Identifizierung herangezogen werden.

(4) Die Fleckgrösse ist von der chromatographierten Substanzmenge weitgehend unabhängig. (Sbst. 5 enthielt nach einer quantitativen Auswertung der Craig-Verteilungskurve des Cannabisextraktes Cannabidiol und Tetrahydrocannabinol

[6] P. Duquenois, *Ann. Med. Légale Crim.* **34**, 224 (1954).
[7] W. Beam, *Fourth Rep. of Wellcome Trop. Res. Labor. Chem. Sect. Khortoum* B 25–26 (1911) Bulletin Nr. 3 (1915); zit. bei R. Weitz und A. Dardanne, *Bull. Sci. Pharm.* **31**, 321 (1942); *C.* II 1255 (1924).
[8] F. G. Fischer und H. Dörfel, Hoppe Seyler's *Z. Physiol. Chem.* **297**, 278 (1954).
[9] J. C. Binzer, Hatzfeld/Eder; C. Schleicher u. Schüll, Dassel Krs. Einbeck.

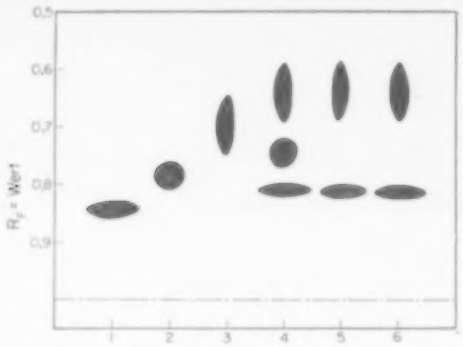


Abb. 1. Chromatogramm von Cannabidiol, Cannabinol und Tetrahydrocannabinol, einzeln und in Gemischen chromatographiert an 2043 a hy (Schleicher u. Schüll) mit dem System Ligroin/Benzol/Chloroform/Methanol/Wasser = 2:2:1:4:1

1 Cannabidiol (CBD)
2 Cannabinol (CBN)
3 Tetrahydrocannabinol (THC)
4 CBD + CBN + THC
5 Extrakt von Cannabis sativa non indica
6 Extrakt von Cannabis sativa indica.

im Konzentrationsverhältnis von 40:1). Es können also auch Cannabinol-Gemische mit ungünstigem Konzentrationsverhältnis chromatographiert werden.

(5) Farbstoffe wie Chlorophyll, Xanthophyll und Carotin bleiben auf der Startlinie zurück und stören daher nicht.

Zur Identifizierung der Flecke auf dem Chromatogramm wurden folgende Verfahren entwickelt:

(1) *Identifizierung durch Farbreaktionen*

Von den zahlreichen, in der Literatur beschriebenen Farbreagentien[10] bewährte sich nur das Reagens nach Beam (Cannabidiol wird blau gefärbt, Cannabinol und Tetrahydrocannabinol bleiben farblos). Weitere empfindliche Farbreagentien sind das Reagens nach Pauly, diazotiertes *p*-Nitranilin[11] sowie 2,6-Dichlorchinonchlorimid,[12] die mit allen drei Cannabinolen gleiche Färbungen geben.

Eine farbliche Differenzierung wird durch kombinierte Anwendung von je zwei der in Tabelle 1 aufgeführten Sprühreagentien ermöglicht. Dazu wird das Chromatogramm nacheinander mit den Komponenten einer Reagenskombination besprüht.

Als besonders geeignet erweisen sich die Kombinationen 1–3, vor allem, wenn neben den Farbreaktionen die Fluoreszenzerscheinungen berücksichtigt werden. Auf dem Chromatogramm zeigen vor dem Besprühen zunächst alle drei Cannabinolverbindungen unter der Analysenquarzlampe eine schwach dunkelblaue Fluoreszenzlöschung; besprüht man mit dem Reagens nach Beam, so ist zunächst Cannabidiol

[10] Zusammenfassende tabellarische Übersicht aller Farbreaktionen für Cannabidiol von R. Adams, M. Hunt und J. H. Clark, *J. Amer. Chem. Soc.* **62**, 196 (1940).
[11] A. Grüne, *Chimia* **11**, 173, 213 (1957).
[12] E. Hoffman und G. Hoffman, *Naturwissenschaften* **45**, 337 (1958) R. Gosh, A. R. Todd, D. C. Wright, *J. Chem. Soc.* 137 (1941).

Tabelle 1

Test-subst. / Sprühreagenskomb.	Tetrahydrocannabinol	Cannabinol	Cannabidiol
1. Beam/Pauly	zitronengelb	ockerbraun	schmutzig dunkelgelb
2. Beam/2,6-Dichl.	kobaltblau (violettstichig)	blaugrün (grüner Rand)	lila
3. Beam/diaz. p-Nitr.	zitronengelb	orange	rotbraun
4. 2,6-Dichl./diaz. p-Nitr.	zitronengelb	ockerbraun	orange
5. 2,6-Dichl./Pauly	kobaltblau	blaugrün	lila

auf Grund der Farbreaktion im Sichtbaren sicher identifizierbar. Auf dem nun alkalischen Chromatogramm wird Cannabinol durch eine stark hellblaue Fluoreszenz erkannt, während Canabinol und Tetrahydrocannabinol unverändert eine Löschung geben. Übersprüht man anschliessend mit Paulys Reagens, diazot. *p*-Nitranilin oder 2,6-Dichlorchinonchlorimid, so erhält man die in Tabelle 1 beschriebenen Färbungen. Danach ist auch Tetrahydrocannabinol sicher nachweisbar. Durch Vergleich zweier mit verschiedenen Reagenskombinationen besprühter Chromatogramme kann die Sicherheit des Verfahrens weiter erhöht werden.

2. *Identifizierung durch Aufnahme der UV-Absorptionsspektren*

Im UV absorbieren in methanolischer Lösung Cannabinol bei 220 und 285 mμ Cannabidiol und Tetrahydrocannabinol bei 212, 273 und 280 mμ.[2] Die unterschiedliche Lage der UV-Absorptionsmaxima kann zur Identifizierung der Cannabinolverbindungen herangezogen werden. Dazu ist besonders das von Korte und Weitkamp[13] beschriebene UV-Messverfahren am Papierchromatogramm geeignet (Tabelle 2).

Die Methode ist sehr empfindlich und gestattet noch den sicheren Nachweis von 5 μg. Eine Verschiebung gegenüber den in Lösung (Methanol) gemessenen Absorptionen findet praktisch nicht statt (siehe Tabelle 2). Die in Methanol für Cannabidiol

Tabelle 2. UV-Absorptionsmaxima der Cannabinolverbindungen

I in Absorption gemessen am Papierchromatogramm mit Beckman Reflectance Unit, Spektrophotometer DK II

II in Durchsicht gemessen in methanolischer Lösung mit einem Spektrophotometer Beckman, Modell DK I

Tetrahydrocannabinol		Cannabinol		Cannabidiol	
I	II	I	II	I	II
nicht messbar 273–281 mμ	212 mμ 273 280	nicht messbar 285 mμ 297 (Schulter)	220 mμ 285 297 (Schulter)	nicht messbar 273–281 mμ	212 mμ 273 280

[13] F. Korte und H. Weitkamp, *Angew. Chem.* **70**, 434 (1958); **71**, 455 (1959).

und Tetrahydrocannabinol registrierbaren Maxima bei 273 und 280 mμ fallen zu einem einzigen Maximum zusammen. Messungen unterhalb 230 mμ sind wegen der Eigenabsorption des Papiers nicht mehr durchführbar. Cannabidiol und Tetrahydrocannabinol zeigen zwar die gleichen UV-Absorptionen; eine Verwechslung ist bei Berücksichtigung der charakteristischen Fleckenform und der sehr unterschiedlichen R_F-Werte jedoch ausgeschlossen.

Eine genaue quantitative Auswertung der Flecke auf dem Papierchromatogramm lässt sich nach den bekannten Verfahren[13,14] nur mit Hilfe von Vergleichschromatogrammen der reinen Cannabinolverbindungen durchführen. Eine ungefähre Gehaltsbestimmung ist dagegen ohne Vergleichschromatogramme möglich, wenn man unterschiedliche Mengen Testsubstanz nebeneinander chromatographiert, die Flecke mit einem Sprühreagens anfärbt und die untere Nachweisgrenze feststellt. Sie liegt bei einer Laufstrecke von 40 cm für das Beam-Reagens bei 10 μg, für Paulys Reagens und diazot. *p*-Nitranilin bei 5 μg und für 2,6-Dichlorchinonchlorimid bei 15 μg. Alle Cannabinole zeigen gegenüber diesen Reagentien die gleiche Empfindlichkeit.

EXPERIMENTELLER TEIL

Es werden folgende Abkürzungen benutzt:

CBD = Cannabidiol, CBN = Cannabinol, THC = Tetrahydrocannabinol

Lösungsmittel. Ligroin (Sdp. 60–95°), Benzol, Chloroform, Methanol und Wasser werden sorgfältig fraktioniert und im Volumenverhältnis von 2:2:1:4:1 ins Gleichgewicht gesetzt.

Apparatur. Als Entwicklungskammern werden rechteckige Glaskästen von 22 cm Länge, 20 cm Tiefe und 60 cm Höhe verwendet. Die Kästen sind mit geschliffenen, absolut dicht aufliegenden Glasplatten bedeckt. In einem Kasten können 6 Streifen von je 5–6 cm oder 2 Streifen von je 15–18 cm Breite gleichzeitig chromatographiert werden. Auf den Boden des Zylinders wird eine Schale mit ca. 50 ml Oberphase gestellt.

Vorbereiten und Entwickeln des Chromatogramms. Ein Bogen Chromatographiepapier (60 × 60 cm) 2043 a hy (Schleicher u. Schüll) wird in Streifen von je 18 cm so zerschnitten, dass die Papierfaserrichtung in der Laufrichtung des Lösungsmittels liegt. Je 40 μg Cannabidiol, Tetrahydrocannabinol und Cannabinol werden in 1%iger petrolätherischer Lösung ca. 8 cm unterhalb des oberen Papierrandes mit einer Mikrosyringe in kleinen Portionen einzeln und als Gemisch (Sbst. 1–4 in Abb. 1) im Abstand von 3 cm nebeneinander aufgetragen. Die Ausdehnung der aufgebrachten Substanzflecke soll 3 mm Durchmesser nicht überschreiten. Eine Gleichgewichtseinstellung durch längeres Einhängen der Streifen in den Dampfraum der organischen Phase ist nicht erforderlich. Temperaturschwankungen von 1–4° während der Chromatographie bleiben ohne sichtbaren Einfluss. Es wird mit der Unterphase absteigend chromatographiert. Die Lösungsmittelfront läuft bei einer Versuchstemperatur von 22 ± 1° in 24 Stdn. 40 cm weit. Die entwickelten Chromatogramme werden 2 Min. bei 80° oder mit dem Heissluftstrom eines Föhns getrocknet.

R_F-Werte

Die Cannabinolverbindungen liefern folgende R_F-Werte:

(a). einzeln chromatographiert (siehe Sbst. 1–3 in Abb. 1)

CBD 0,84, CBN 0,79, THC 0,70

(b). als Gemisch chromatographiert (siehe Sbst. 4 in Abb. 1)

CBD 0,81, CBN 0,75 THC 0,64.

[14] H. F. Linskens, *Papierchromatographie in der Botanik* S. 174, 2. Aufl., Berlin, Göttingen, Heidelberg (1959).

Farbreaktionen

(a) *Allgemeine Technik.* Das Chromatogramm wird auf holzfreies Fliesspapier gelegt, an beiden Enden durch Gewichtsstücke gespannt und bei Verwendung wässriger Entwicklerlösungen (Reagens nach Pauly, bzw. diazot. *p*-Nitranilin) so stark besprüht, dass es von einer gleichmässig dünnen Flüssigkeitsschicht völlig bedeckt ist. Für einen Streifen von 6 × 50 cm werden ca. 20 ml benötigt. Ein Verlaufen der Flecke ist auch bei starkem Einsprühen nicht zu befürchten. Die nicht wässrigen Reagens-Lösungen (Beam-Reagens und 2,6-Dichlorchinonchlorimid) werden dagegen vorsichtiger und in geringeren Mengen (ca. 5 ml) aufgesprüht. 1 Min. einwirken lassen und den Überschuss mit holzfreiem Fliesspapier gleichmässig ablöschen. Die Behandlung wird von der anderen Seite in der gleichen Weise wiederholt.

(b) *Einzelanfärbungen.* Reagens nach Beam (5%ige Lösung von KOH in Äthanol): Das entwickelte Chromatogramm wird gemäss der unter (a) angegebenen Technik mit dem Reagens nach Beam angesprüht und 5 Min. bei 105° erhitzt. CBD wird blau gefärbt. Untere Nachweisgrenze 20 μg. Unter der Analysenquarzlampe mit Filter für 255 mμ erhält man für CBD und THC eine schwach dunkelblaue Fluoreszenzlöschung (untere Nachweisgrenze 40 μg), für CBN eine starke hellblaue Fluoreszenz (untere Nachweisgrenze 10 μg). Im langwelligen UV (Filter für 360 mμ) keine Fluoreszenz oder Löschung.

Paulys Reagens (p-*Diazobenzolsulfonsäure*). Kurz vor dem Besprühen werden 0,1 g *p*-Diazobenzolsulfonsäure in 20 ml 10%iger Na_2CO_3-Lösung gelöst. Die Reagenslösung ist 20 Min. haltbar. Nach dem Besprühen liegt die Lösung tropfenförmig auf dem Papier. Alle Cannabinole geben gleichmässig ockerbraune Flecke. Untere Nachweisgrenze 5 μg. Untergrundfarbe weiss.

Diazot. p-*Nitranilin.* 25 ml einer 0,3%igen Lösung von *p*-Nitranilin in 8% HCl werden mit 1,5 ml einer 5%igen $NaNO_2$-Lösung gemischt. Die Reagenslösung ist ca. 1 Woche haltbar. Das besprühte Chromatogramm wird unter fliessendem Leitungswasser von beiden Seiten ca. 5 sec. gewaschen. Die Flecke sind wasserunlöslich und verlaufen nicht. Diese Technik hat vor dem in der Literatur angegebenen Besprühen des Chromatogramms mit 20%iger Sodalösung den Vorteil, dass die Untergrundfarbe weiss bleibt und die ockerbraune Farbe der Cannabinolderivate besser hervortritt. Unter Nachweisgrenze 5 μg.

2,6-*Dichlorchinonchlorimid.* Das Chromatogramm wird mit einer 0,3%igen methanolischen Lösung von 2,6-Dichlorchinonchlorimid angesprüht und 10 Min. bei 80–105° getrocknet. Alle drei Cannabinolverbindungen geben sehr beständige rosa, violettstichige Flecke. Untergrundfarbe weiss. Nachweisgrenze 15 μg.

(c) *Differenzierende Anfärbung* (siehe Tabelle 2). Die Flecke werden zunächst mit dem an erster Stelle angeführten Reagens nach der unter (a) und (b) beschriebenen Technik angefärbt. Dann wird mit dem zweiten Reagens übersprüht.

Kombination Beam/Pauly. Mit dem Reagens nach Beam werden zunächst CBD und CBN identifiziert. Nach dem Übersprühen mit Paulys Reagens färbt sich CBD schmutzig gelb, CBN ockerbraun und THC zitronengelb. THC hebt sich farblich gut von CBN ab. Untere Nachweisgrenze 10 μg. Untergrundfarbe weiss. Die angefärbten Chromatogramme sind lange ohne sichtbare Veränderung haltbar.

Beam/2,6-Dichlorchinonchlorimid. Anfärben nach Beam in der oben beschriebenen Weise, dann Übersprühen mit 2,6-Dichlorchinonchlorimid. CBD färbt sich lila, CBN blaugrün (grüner Rand), THC kobaltblau (violettstichig). Untergrundfarbe graubraun. Die Farben sind unmittelbar nach dem Besprühen besonders stark (untere Nachweisgrenze 2 μg), verblassen aber sehr schnell etwas (untere Nachweisgrenze 10 μg). Nach 5 Min. Erhitzen bei 105° findet keine Änderung der Farbintensität mehr statt. Die angefärbten Chromatogramme sind lange ohne sichtbare Veränderung haltbar.

Diazot. p-*Nitranilin/Beam.* Chromatogramm mit diazot. *p*-Nitranilin anfärben und ohne vorheriges Neutralisieren oder Auswaschen mit dem Reagens nach Beam übersprühen. CBD färbt sich braun, CBN braunviolett und THC rotviolett. Die Farben sind nur wenige Minuten beständig. Sie gestatten zunächst eine sichere Unterscheidung zwischen CBD und CBN/THC. Nach 10 Min. Erhitzen bei 105° färbt sich CBD braunviolett, CBN braun und THC zitronengelb. Die Farben erlauben nun eine Unterscheidung zwischen THC und CBN/CBD. Die Farben verändern langsam etwas ihre Tönung. Untere Nachweisgrenze 10 μg.

2,6-*Dichlorchinonchlorimid/diazot.* p-*Nitranilin.* Chromatogramm mit 2,6-Dichlorchinonchlorimid ansprühen, 5 Min. bei 105° erhitzen, dann mit diazot. *p*-Nitranilin übersprühen. Reagens

1 Min. einwirken lassen, dann mit fliessendem Leitungswasser waschen. CBD färbt sich orange, CBN ockerbraun, THC zitronengelb. THC hebt sich farblich gut von CBN und CBD ab. Untergrundfarbe weiss. Untere Nachweisgrenze 5 μg. Die Farben sind mindestens 4 Wochen ohne Veränderung haltbar.

2,6-*Dichlorchinonchlorimid/Pauly*. Chromatogramm mit 2,6-Dichlorchinonchlorimid besprühen, 5 Min. bei 105° erhitzen, dann mit Paulys Reagens übersprühen. Reagens 1 Min. einwirken lassen, dann ablöschen. CBD färbt sich lila, CBN blaugün, THC kobaltblau. Untergrundfarbe graubraun. Untere Nachweisgrenze 10 μg.

Wir danken der Research Corporation, New York und der Deutschen Forschungsgeminschaft, Bad Godesberg, herzlich für eine Sachbeihilfe.

VOL. 10 1960

Tetrahedron, 1960, Vol. 10, pp. 160 to 163. Pergamon Press Ltd. Printed in Northern Ireland

TOXIC FLUORINE COMPOUNDS CONTAINING THE C—F LINK—XI*

LABILITY OF THE FLUORINE ATOM IN 2-FLUOROETHANOL

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(*Received* 30 *March* 1960)

Abstract—It has been shown that 2-fluoroethanol, often described as a chemically unreactive compound, will react with a number of nucleophilic reagents.

In Part X of this series[1] we gave experimental evidence to show that, although the C—F link in fluoroacetic acid is often correctly described as strong, there are many reactions in which this bond is easily broken. Thus whereas boiling 10 per cent aqueous sodium hydroxide is without effect on the C—F link in fluoroacetic acid, boiling 30 per cent aqueous sodium hydroxide will give a quantitative elimination of F^-. Similarly Grignard reagents will rupture certain C—F links giving well-defined products. Thus methyl fluoroacetate reacts with phenyl magnesium bromide to give triphenylethanol and methyl γ-fluorobutyrate gives 2,2-diphenyltetrahydrofuran.

It has often been stated that the C—F link in 2-fluoroethanol is a firm one, although very little precise evidence has been produced in support of this observation. It is claimed that in fluoroethanol, "the fluorine atom is unaffected by all but the most drastic treatment".[2] McCabe and Warner[3] observed that the reaction between fluoroethanol and hydroxyl ion is so slow that the solvent media effects were studied only at 60°. They were, however, able to show the presence of ethylene oxide in the resulting solution. Without giving any details of concentrations used, Swarts[4,5] made passing reference to the fact that 2-fluoroethanol is attacked by alkali whereas sodium fluoroacetate gave no F^- under the conditions of his experiment.

Our interest in the reactivity of the fluorine atom in 2-fluoroethanol was stimulated by the observation that a pure sample of the compound, left in a bottle for several years, gave the iodoform reaction in the cold and a positive test for the fluoride ion. Freshly distilled fluoroethanol does not give the iodoform reaction.[6] Moreover ethylene chlorohydrin, left under similar conditions and for a similar period does not give an immediate iodoform reaction in the cold nor does it give a positive test for chloride ion.

The evidence accumulated so far points to the fact that iodoform is produced from

* Part X: P. Mirosevic-Sorgo and B. C. Saunders, *Tetrahedron* **5**, 38 (1959).

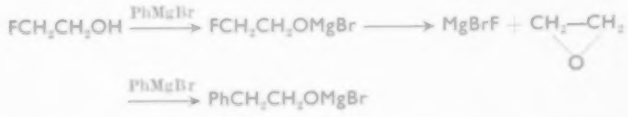
[1] P. Mirosevic-Sorgo and B. C. Saunders, *Tetrahedron* **5**, 38 (1959).
[2] F. L. M. Pattison, *Toxic Aliphatic Compounds* p. 24. Elsevier, Amsterdam (1959).
[3] C. L. McCabe and J. C. Warner, *J. Amer. Chem. Soc.* **70**, 4031 (1948).
[4] F. Swarts, *Bull. Acad. Roy. Belg.* **7** (1914).
[5] F. Swarts, *J. Chim. Phys.* **17**, 3 (1919).
[6] C. C. Price and W. G. Jackson, *J. Amer. Chem. Soc.* **69**, 1065 (1947).

acetaldehyde formed by the rearrangement of ethylene oxide obtained by the dehydrofluorination of fluoroethanol:

Support for this mechanism is also provided by an earlier observation by Saunders and Stacey,[7] who noted that, in the preparation of fluoroethanol from ethylene chlorohydrin and potassium fluoride, crotonaldehyde is always produced as an impurity. This is readily explained on the basis of the initial production of acetaldehyde according to the above equation.

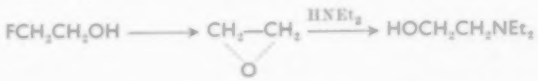
Details are given in the Experimental of a procedure that has enabled us to demonstrate the presence of both ethylene oxide and acetaldehyde in the reaction product obtained by action of very concentrated sodium hydroxide solution on fluoroethanol. It has also been shown that fluoroethanol is sensitive to *cold* aqueous alkali. When, for example, fluoroethanol was allowed to stand at room temperature for 12 hours with 10 per cent sodium hydroxide solution, 80 per cent of the fluoride appeared as fluoride. In these circumstances, the C—F link in methyl fluoroacetate was not affected.[1]

On heating 2-fluoroethanol with phenyl magnesium bromide in ether, the fluorine atom was eliminated and phenylethanol resulted. The reaction most probably follows the course.



On heating 2-fluoroethanol with sodium phenoxide, 2-phenoxyethanol was obtained. Using similar conditions sodium thiophenoxide gave a 64 per cent yield of 2-hydroxyethyl phenyl sulphide, and sodium sulphide gave a 60 per cent yield of di(2-hydroxyethyl) sulphide. Attempts to obtain ethylene cyanhydrin from 2-fluoroethanol and sodium cyanide were not successful for under mild conditions no reaction occurred, whereas heating under reflux resulted in a vigorous reaction with the evolution of ammonia owing to the hydrolysis of the cyanhydrin first formed. Under these conditions 60 per cent of the fluorine of the fluoroethanol appeared as fluoride ion.

When a mixture of diethylamine and 2-fluoroethanol was heated for as long as 24 hours no reaction took place. However, when the amine and fluoroethanol were allowed to react in the presence of 0·5 mole of sodium hydroxide for only 40 minutes 2-hydroxyethyl diethylamine was obtained in 40 per cent yield. It is evident that in this case ethylene oxide is first formed by the action of the alkali on fluoroethanol, and subsequently reacts with diethylamine.



Thioglycollic acid reacted very readily with fluoroethanol when heated together under reflux in the presence of alkali, the product being hydroxyethylthioglycollic acid.

[7] B. C. Saunders, G. J. Stacey and I. G. E. Wilding, *J. Chem. Soc.* 773 (1949).

No significant reactions were observed between 2-fluoroethanol and potassium phthalimide, sodium *p*-toluenesulphonate, potassium thiocyanate, sodiom diethyl malonate, piperidine and thiourea.

It may be concluded that aliphatic fluorine compounds containing the C—F link are in general relatively unstable if they are able to lose hydrogen fluoride and form an intermediate oxide-ring compound. It can be expected that compounds which, like 2-fluoroethanol, have fluorine and hydroxyl groups on adjacent carbon atoms will lose hydrogen fluoride fairly readily.

In this connexion the relative instability of fluoroacetid acid to concentrated alkali should be considered in relation to the work of Grunwald and Winstein[8] who suggested "α-lactone" formation for other monohalogeno-carboxylic acids.

EXPERIMENTAL

All experiments were carried out in a fume-cupboard fitted with a powerful fan.

The action of concentrated sodium hydroxide solution on 2-fluoroethanol. 2-Fluoroethanol (32 g, 0·5 mole) was placed in a three-necked flask fitted with a stirrer and reflux condenser. The outlet of the condenser was fitted with glass tubing leading to an acetone-solid carbon dioxide trap. Conc sodium hydroxide solution (40 g, 1·0 mole in 40 ml water) was added dropwise with vigorous stirring. When about half of the sodium hydroxide solution had been added, a very vigorous reaction ensued. When this had moderated, the remainder of the sodium hydroxide solution was added during 10 min. The liquid (6 g) that collected in the trap was shown to be a mixture of ethylene oxide and acetaldehyde as follows. To the liquid (1 g) were added (a) cold conc hydrochloric acid (5 ml) and (b) 2,4-dinitrophenylhydrazine reagent (5 ml). The first reagent yielded ethylene chlorohydrin identified as its 1-naphthylurethane, m.p. 100° (lit. 101°). (Found: C, 62·2; H, 5·0; N, 5·4. Calc. for $C_{13}H_{12}ClNO_2$: C, 62·3; H, 4·85; N, 5·6%). The second reagent (b) yielded acetaldehyde 2,4-dinitrophenylhydrazone, m.p. 148° (lit. 148°, 168°). (Found: C, 42·7; H, 3·9; N, 25·5. Calc. for $C_8H_8N_4O_4$: C, 42·9; H, 3·6; N, 25·0%).

Reaction between 10% aqueous sodium hydroxide solution and 2-fluoroethanol. 2-Fluoroethanol (1·2 g) and 10% aqueous sodium hydroxide solution (20 ml) were mixed and allowed to stand overnight at 20°. The solution was then made up to 100 ml with distilled water and aliquot portions of 10 ml were titrated using thorium nitrate solution.[9] Results showed that 84·5 ± 0·5% of fluoroethanol had been hydrolysed to F^-.

Reaction between phenyl magnesium bromide and 2-fluoroethanol. Phenyl magnesium bromide was made from bromobenzene (157 g, 1 mole) and magnesium (24·3 g) in ether (500 ml). After allowing to cool, fluoroethanol (19·3 g, 0·3 mole) in ether (100 ml) was added slowly with stirring. A vigorous reaction took place causing the ether to boil. After all the fluoroethanol had been added and the reaction had subsided, the mixture was heated under reflux for 30 min and set aside overnight. The product was poured on to ice (1 kg) and conc hydrochloric acid (200 ml). After stirring, the aqueous layer (A) was separated, and the ethereal layer was dried ($MgSO_4$) and the ether distilled off. The residue was distilled under reduced pressure and gave small quantities of diphenyl, bromobenzene and terphenyl and a fraction of b.p. 108–115°/20 mm (5 g, 13·5%). This proved to be 2-phenylethanol and was converted into its 1-naphthylurethane, m.p. 118·5–119·5° (lit. 119°). (Found: C, 79·2; H, 6·3; N, 4·85. Calc. for $C_{19}H_{17}NO_2$: C, 79·4; H, 6·0; N, 4·8%).

A fluoride determination on the aqueous layer (A), using the thorium nitrate method,[9] showed that 82% of the fluoroethanol had been converted to F^-.

Sodium phenoxide and 2-fluoroethanol. Phenol (47 g, 0·5 mole) was dissolved in a slight excess of sodium hydroxide solution (70 ml, 30%), and fluoroethanol (32 g, 0·5 mole) was added. The mixture was heated under reflux. After about 10 min the reaction became very vigorous and the heating was discontinued for a few minutes. Sodium fluoride gradually separated. When the reaction had subsided, the heating was continued, making a total of 30 min in all. After allowing to cool overnight, the liquid was decanted and extracted with ether (2 × 200 ml) and dried ($MgSO_4$). The ether was

[8] E. Grunwald and S. Winstein, *J. Amer. Chem. Soc.* **70**, 841 (1948).

[9] B. C. Saunders, *Some aspects of the Chemistry and Toxic Action of Organic Compounds Containing Phosphorus and Fluorine* p. 210. Cambridge University Press, London (1957).

removed and the residue distilled giving a fraction of b.p. 135–160°/40 mm. This was refractionated and then had b.p. 83–85°/0·3 mm (38 g, 55%). (Found: C, 69·9; H, 7·1. Calc. for $C_8H_{10}O_2$: C, 69·6; H, 7·3%). This 2-phenoxyethanol was converted into its 1-naphthylurethane, m.p. 124°. (Found: C, 73·7; H, 6·2; N, 4·8. Calc. for $C_{19}H_{17}NO_3$: C, 74·2; H, 5·7; N, 4·6%).

Sodium thiophenoxide and 2-fluoroethanol. The conditions employed were similar to those given in the previous reaction. Thiophenol (22 g, 0·2 mole) dissolved in sodium hydroxide solution (27 ml, 30%) and 2-fluoroethanol (12·8 g, 0·2 mole) were used. 2-Hydroxyethyl phenyl sulphide was obtained as a fraction of b.p. 100–102°/0·3 mm (19·3 g, 63·5%). (Found: C, 61·8; H, 6·6; S, 20·85. Calc. for $C_8H_{10}OS$: C, 62·3; H, 6·5; S, 20·8%). This was converted into its 1-naphthylurethane, m.p. 69–70°. (Found: C, 71·1; H, 5·9; N, 4·5. Calc. for $C_{19}H_{17}NO_2S$: C, 70·6; H, 5·3; N, 4·3%).

Sodium sulphide and 2-fluoroethanol. Sodium sulphide (80 g of $Na_2S.9H_2O$, 0·5 mole) was dissolved in water (100 ml) and 2-fluoroethanol (32 g, 0·5 mole) added. The mixture was heated under reflux. Heating was discontinued after a few minutes to prevent the violent reaction from getting out of control. Solid was precipitated. When the reaction had moderated, the heating was continued; the total time being ½ hr. After allowing to cool, the liquid (A) was decanted from the solid (B), and water evaporated from (A) under reduced pressure (30–40 mm) on a boiling water bath. The solid and liquid remaining from (A) were added to the original solid (B, also dried) and extracted with hot absolute ethanol (2 × 300 ml), and filtered (the solid residue was predominantly sodium fluoride). The ethanol was distilled off and the fraction, b.p. 160–163°/13 mm of di(2-hydroxyethyl) sulphide was collected and redistilled at b.p. 110°/0·05 mm (18·2 g, 59·6%). (Found: C, 39·3; H, 8·4; S, 25·6. Calc. for $C_4H_{10}O_2S$: C, 39·3; H, 8·3; S, 26·2%).

Sodium cyanide and 2-fluoroethanol. Water (10 ml) and sodium cyanide (25 g, 0·51 mole) were stirred together and 2-fluoroethanol (32 g, 0·5 mole) was added. The mixture was heated under reflux and stirred vigorously. After about 15 min the reaction became violent and heating was discontinued. The mixture continued to boil without further heating for about ½ hr, ammonia being evolved. The mixture, after cooling was extracted with water and ether. The ethereal layer was dried (Na_2SO_4) and shown to contain no ethylene cyanohydrin. A fluoride determination on the aqueous layer showed that at least 60% of the total fluorine had been converted to F^-.

Diethylamine and 2-fluoroethanol. 2-Fluoroethanol (32 g, 0·5 mole) and diethylamine (73 g, 1 mole) were placed in a flask fitted with a very efficient reflux condenser. Sodium hydroxide (20 g, 0·5 mole) in water (20 ml) was added. After about 5 min the mixture began to boil without the application of external heating and continued to do so for 45 min, sodium fluoride separated out meanwhile. After cooling, the mixture was extracted with benzene (200 ml) filtered and dried (K_2CO_3). After distilling off the benzene, the 2-hydroxyethyl diethylamine, b.p. 50–60°/15 mm was collected. It redistilled at b.p. 58–62°/15 mm (23·8 g, 41%). The picrate was recrystallized from ethanol and had m.p. 78° (lit. 79°). (Found: N, 16·2. Calc. for $C_{12}H_{18}N_4O_8$: N, 16·2%).

Thioglycollic acid and 2-fluoroethanol. A mixture of thioglycollic acid (9·4 g, 0·1 mole), sodium hydroxide (8 g, 0·2 mole) in water (80 ml) and 2-fluoroethanol (6·4 g, 0·1 mole) was heated under reflux for 1 hr. After cooling and filtering, copper acetate (9·1 g, 0·5 mole) in water (200 ml) was added. After 12 hr the liquid was decanted from the magnificent dark blue crystals of copper hydroxyethylthioglycollate which had separated. These were washed with water and dried *in vacuo* and were still contaminated with traces of copper thioglycollate. (13·8 g, 82·5%) (Found: C, 27·95; H, 4·3; S, 19·95. Calc. for $C_8H_{14}O_6S_2Cu$: C, 28·8; H, 4·2; S, 19·2%).

Acknowledgement—One of us (D. L. E. B.) is indebted to the Department of Scientific and Industrial Research for a maintenance allowance.

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Tetrahedron, 1960, Vol. 10, pp. 164 to 170. Pergamon Press Ltd. Printed in Northern Ireland

5,5,5-TRIFLUOROLAEVULIC ACID AND SOME DERIVED COMPOUNDS

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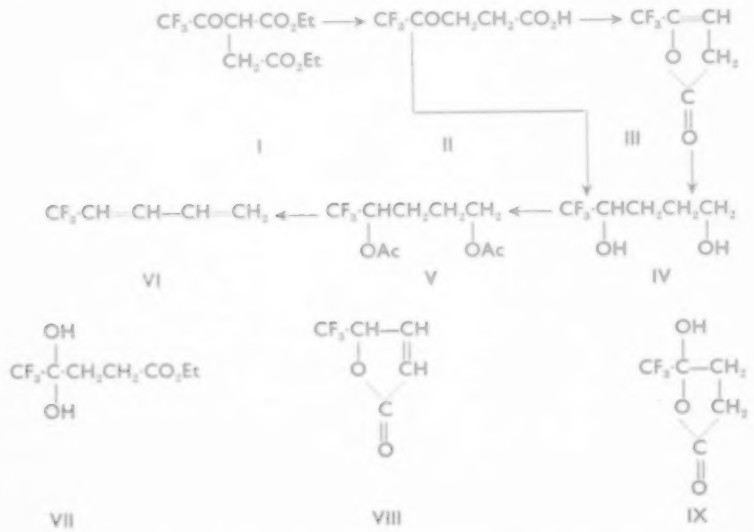
(*Received* 2 *April* 1960)

Abstract—5,5,5-Trifluorolaevulic acid (II) has been prepared by the acidic hydrolysis of the Claisen condensation product (I) of ethyl trifluoroacetate and diethyl succinate. Dehydration of the acid (II) with phosphoric oxide gave 4-hydroxy-5,5,5-trifluoropent-3-enoic acid lactone (III). Reduction of either this lactone or the acid (II) with lithium aluminium hydride gave 5,5,5-trifluoropentane-1,4-diol (IV), from which 5,5,5-trifluoropenta-1,3-diene (VI) has been obtained by acetylation followed by pyrolysis.

A RECENT publication by Groth,[1] which describes *inter alia* compounds derived from the Claisen condensation of ethyl trifluoroacetate and diethyl succinate, prompts us to publish our related, but more detailed, work on this topic. The main reactions which we have carried out are summarized below.



Groth[1] did not isolate diethyl trifluoroacetosuccinate (I) but instead, converted it, by acidic hydrolysis into an unsaturated lactone to which he assigned the structure VIII. He hydrogenated this material to give a saturated lactone which he condensed further with ethyl trifluoroacetate.

Three catalysts appear to have been employed to effect Claisen condensations of

[1] R. H. Groth, *J. Org. Chem.* **24**, 1709 (1959).

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fluoro-esters. The usual one is sodium ethoxide; sodium hydride has also found application[2] and metallic sodium in one case.[3] In other work in this Department[4] we have found that sodium metal can be used generally for promotion of ester condensations with fluoro-esters. In the present study, all three reagents have been used to condense ethyl trifluoroacetate and diethyl succinate (Groth used sodium ethoxide only). All three catalysts gave the same product from the condensation, diethyl trifluoroacetosuccinate (I). Sodium was the best, it was easiest to use and gave the highest yield, 72 per cent of I. This boiled over a range (100–150°/0·5 mm); all the material appeared, however, to be diethyl trifluoroacetosuccinate, since the yields of the derived acid (II), which were obtained by hydrolysis of low- and high-boiling fractions, were almost identical with that obtained from material boiling over the complete range. This wide boiling-range may have been due to keto-enol tautomerism in I, presumably the lower-boiling material being mainly the enol-isomer, and the higher the keto. This was supported by infra-red spectroscopic analysis: the intensity of the —O—H stretching frequency at 3400 cm^{-1} relative to that of the —C=O stretching frequency at 1850–1700 cm^{-1} being greater in a low-boiling fraction than in a high.

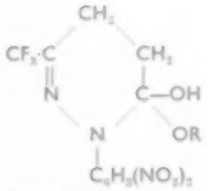
Acidic hydrolysis of the Claisen ester (I) led to two products: the major one was the crystalline 5,5,5-trifluorolaevulic acid (II) and the minor its ethyl ester hydrate (VII). The structure of the acid (II) was confirmed by treatment with alkali when succinic acid was formed by a haloform reaction. The structure of the ester (VII) was demonstrated by hydrolysis to the parent acid (II), and by synthesis from this acid (II) by esterification with ethanol and sulphuric acid. Further confirmation was supplied by conversion of the ester (VII) into the diol (IV) and into the unsaturated lactone (III) (see later). That the ester was hydrated and the acid (II) was not is rather surprising. It is well-known[5] that carbonyl groups flanked by perfluoroalkyl groups form addition compounds easily, so the formation of the ester hydrate (VII) is not unexpected. It is possible, however, that the acid actually has a cyclic structure (IX)—similar cyclic structures have been proposed[6] for derivatives of laevulic acid itself. In the absence of some such addition at the carbonyl group it is difficult to explain the failure of the acid to form a hydrate. It is perhaps significant that the S-benzylthiuronium salt of the acid (II) is hydrated.

Prolonged heating of the acid (II) gave an unsaturated lactone which we consider to be 4-hydroxy-5,5,5-trifluoropent-3-enoic acid lactone (III), the trifluoro-analogue of α-angelicalactone. Other, non-fluorinated γ-keto-acids are known[7] to dehydrate analogously. This unsaturated lactone (III) is, however, best prepared by distillation of the acid (II) from phosphoric oxide or from concentrated sulphuric acid. Groth[1] has suggested the alternative $\alpha\beta$-unsaturated structure (VIII) for this product: he compared its behaviour towards catalytic hydrogenation, aniline, ethanolic hydrogen chloride and bromine water with the known[8] behaviour of the unfluorinated analogues of III and VIII (α- and β-angelicalactone, respectively). In these tests the fluorinated

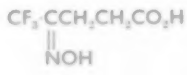
[2] E. T. McBee, O. R. Pierce, H. W. Kilbourne and E. R. Wilson, *J. Amer. Chem. Soc.* **75**, 3152 (1953); F. W. Swamer and C. R. Hauser, *Ibid.* 72, 1352 (1950).
[3] R. N. Haszeldine, W. K. R. Musgrave, F. Smith and L. M. Turton, *J. Chem. Soc.* 609 (1951).
[4] J. Burdon, V. C. R. McLoughlin and J. C. Tatlow, to be published,.
[5] W. K. R. Musgrave, *Quart. Rev.* **8**, 331 (1954).
[6] E. H. Rodd, *The Chemistry of Carbon Compounds* Vol. 1B, p. 879. Elsevier, Amsterdam (1952).
[7] L. Wolff, *Liebigs Ann.* **229**, 249 (1885).
[8] F. A. Kuehl, R. P. Linstead and B. A. Orkin, *J. Chem. Soc.* 2213 (1950); W. A. Jacobs and A. B. Scott, *J. Biol. Chem.* **87**, 601 (1930).

lactone showed a greater similarity towards β-angelicalactone than towards the α-isomer. Contrariwise, however, we have shown that the fluorinated lactone gives two tests which are given[8] by α-angelicalactone but not by β: it affords a silver mirror with ammoniacal silver nitrate and a deep red colour with alkaline nitroprusside solution. It seems probable that the trifluoromethyl group so modifies the chemical properties of structures such as the angelicalactones that any deductions based on such analogies are invalid. Our fluorinated lactone (III) had almost no absorption in the ultra-violet whereas the $\alpha\beta$-unsaturated structure (VIII) would show a large absorption (β-angelicalactone has[9] ε, 10,000 at 214 mμ). Again, the acidic hydrolysis of the fluorinated lactone (III) gave the laevulic acid (II) and lithium aluminium hydride reduction of it gave the diol (IV); neither reaction seems very likely on the basis of structure VIII. It is also difficult to see how the $\alpha\beta$-compound (VIII) could form except by a prototropic rearrangement of the $\beta\gamma$-compound (III), itself formed by simple dehydration of the enol of the acid (II): such rearrangements are usually very slow in acidic media.[10] We therefore suggest that the fluorinated lactone is, in fact, the $\beta\gamma$-unsaturated compound (III). Attempts at dehydration of the hydrated ester (VII) gave mixtures of the unsaturated lactone (III) and starting material. No anhydrous ester could be isolated.

Both the acid (II) and the lactone (III) reacted with aqueous ethanolic 2,4-dinitrophenylhydrazine to give the same product—probably the pyridazone derivative (IX). This could be produced by cyclization of the initially formed 2,4-dinitrophenylhydrazone, followed by addition of ethanol across the carbonyl group. Similar cyclizations[11] occur with non-fluorinated γ-keto-acids. In confirmation of this structure, when the reaction was conducted in aqueous propanol the acid (II) gave the analogous propanol adduct (X). Both the acid and the lactone gave the normal oxime (XI).



IX R = C_2H_5
X R = C_3H_7



XI

Reduction of either the acid (II), the ester (VII) or the lactone (III) with lithium aluminium hydride in ether gave an excellent yield of 5,5,5-trifluoropentane-1,4-diol (IV), although in the case of the lactone (III) a small amount of another, higher-boiling material, whose structure was not investigated, was also formed. The diol (IV) was characterized as its bis (3,5-dinitrobenzoate) and its diacetate (V). The latter compound underwent pyrolysis at 520° to give 5,5,5-trifluoropenta-1,3-diene (VI) in 75 per cent yield. The five-stage synthesis of 1-trifluoromethylbutadiene (VI) described here gives an overall yield of about 33 per cent from ethyl trifluoroacetate. Henne *et al.*[12,13] have obtained about a 39 per cent yield from ethyl trifluoroacetate in

[9] L. J. Haynes and E. R. H. Jones, *J. Chem. Soc.* 954 (1946).
[10] C. K. Ingold, *Structure and Mechanism in Organic Chemistry* pp. 546–550. G. Bell, London (1953).
[11] Reference 6, p. 882.
[12] A. L. Henne, M. S. Newman, L. L. Quill and R. A. Staniforth, *J. Amer. Chem. Soc.* **69**, 1819 (1947).
[13] A. L. Henne and P. E. Hinkamp, *J. Amer. Chem. Soc.* **76**, 5147 (1954).

a four-stage synthesis via 1,1,1-trifluoropentane-2,4-dione, which was reduced to the analogous diol, the acetate of which was pyrolysed.

Treatment of the diene (VI) with bromine in glacial acetic acid gave a dibromo-compound. This appeared to be a single substance since it showed only one (sharp) peak in gas-phase chromatography: its infra-red spectrum also was not suggestive of a mixture. The complete absence of any strong absorption in the region 900–950 cm^{-1} showed[14] that the compound possessed no vinyl (—CH=CH_2) group, and was not, therefore, the 1,2-dibromo-compound. We have not, however, been able to distinguish between the other two possibilities, the 1,4- and 3,4-compounds. Oxidation led only to small yields (<10 per cent) of trifluoroacetic acid—too low to be of any significance.

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EXPERIMENTAL

The condensation of ethyl trifluoroacetate with diethyl succinate

(a) *With sodium hydride as catalyst.* Ethyl trifluoroacetate (96·5 g, 0·68 mole) was added to powdered sodium hydride (17·0 g, 0·71 mole) over a period of about 10 min in an atmosphere of dry nitrogen. When reaction had subsided, the viscous solution was heated to 60° and diethyl succinate (48·5 g, 0·28 mole) was added, with stirring, over 5–6 hr; the resulting mixture was maintained at 65–70° and was stirred vigorously for a further 15 hr. The reaction mixture was allowed to cool and crushed ice (ca. 100 g) was added to it, followed by water (100 ml) and sulphuric acid (50 ml, *d*, 1·84). The oily product was extracted with ether (3 × 100 ml), the extracts were dried ($MgSO_4$) and the ether was evaporated to leave crude *diethyl trifluoroacetosuccinate* (I, 55·5 g), b.p. 78–113°/0·5 mm, n_D^{19} 1·4070. This material contained diethyl succinate (ca. 3 g) since hydrolysis (see below) gave some succinic acid. When a smaller proportion of ethyl trifluoroacetate was used, greater amounts of diethyl succinate remained unreacted. Fractional distillation of this crude product under reduced pressure was unsatisfactory since only a very low boil-up rate could be achieved; this caused the reflux temperature to fluctuate widely. A pure product (Found: C, 44·6; H, 4·8. $C_{10}H_{13}F_3O_5$ requires: C, 44·5; H, 4·9%) was, however, obtained as a middle fraction.

(b) *With sodium ethoxide as catalyst.* A mixture of sodium ethoxide (63·5 g, 0·93 mole), ethyl trifluoroacetate (88·7 g, 0·62 mole) and diethyl succinate (48·5 g, 0·28 mole) was refluxed in dry ether for 16 hr. Isolation as in (a) gave crude diethyl trifluoroacetosuccinate (I, 11·9 g), n_D^{19} 1·4118. Groth[1] converted this crude product directly into the lactone (III or VIII) in 33–39% yield overall.

(c) *With sodium as catalyst.* Sodium wire (5·0 g, 0·22 mole), ethyl trifluoroacetate (31 g, 0·22 mole) and diethyl succinate (76 g, 0·44 mole) were mixed and then heated to 80° until reaction commenced, when the source of heat was removed. The reaction continued until all the sodium had dissolved. Dry ether (60 ml) was added and the solution was refluxed for 18 hr. The ether and excess of diethyl succinate were then distilled off, the latter *in vacuo*, to leave a black tarry residue of sodio-derivative. The free keto-ester was liberated by treatment with sulphuric acid (150 ml, 10 N) and was extracted with ether (6 × 50 ml). Distillation of the dried ($MgSO_4$) extracts gave crude diethyl trifluoroacetosuccinate (I, 42 g), b.p. 100–150°/0·5 mm, n_D^{20} 1·4104, shown by infra-red spectroscopy to be identical with the product prepared in (a). This crude material was used without further purification in the hydrolysis experiments.

Acidic hydrolysis of diethyl trifluoroacetosuccinate (I)

The ester [42 g, prepared as in (c), above] was refluxed with sulphuric acid (270 ml, 40% w/w) for 4 hr. After being cooled, the solution was extracted with ether (6 × 60 ml) and the extracts were dried ($MgSO_4$) and the ether evaporated. Distillation of the residue *in vacuo* gave (i) *ethyl 5,5,5-trifluorolaevulate hydrate* (VII, 3·5 g), b.p. 40–42°/0·1 mm, n_D^{18} 1·3725 (Found: C, 38·7; H, 4·9. $C_7H_9F_3O_3{\cdot}H_2O$ requires: C, 38·9; H, 5·1%), and (ii) crude *5,5,5-trifluorolaevulic acid* (II, 20 g), b.p. 68–72°/0·1 mm, n_D^{22} 1·3900, which solidified, m.p. 54–56°, and after crystallization from benzene had m.p. 57–58° (17·6 g) (Found: C, 35·2; H, 2·8; equiv., 171. $C_5H_5F_3O_3$ requires: C, 35·3; H, 3·0%; equiv., 170). Under the same conditions, hydrolysis of a fraction b.p. 77–85°/0·15 mm

[14] L. J. Bellamy, *The Infra-red Spectra of Complex Molecules* p. 34. Methuen, London (1958).

(10 g) gave ester hydrate (0·68 g) and acid (4·7 g); a fraction b.p. 114–120°/0·15 mm (10 g) gave ester hydrate (0·57 g) and acid (4·9 g).

Treatment of an aqueous solution of the neutralized acid with a conc aqueous solution of S-benzylthiuronium chloride gave S-*benzylthiuronium* 5,5,5-*trifluorolaevulate hydrate*, m.p. 119° (from acetone–chloroform) (Found: C, 43·7; H, 5·1. $C_{13}H_{15}F_3N_2O_3S{\cdot}H_2O$ requires: C, 44·1; H, 4·8%).

Acidic hydrolysis of ethyl 5,5,5-*trifluorolaevulate hydrate* (VIII)

The ester hydrate (2·0 g) was refluxed with sulphuric acid (20 ml, 40% w/w) for 17 hr. Isolation by ether extraction (5 × 10 ml) gave 5,5,5-trifluorolaevulic acid (II, 1·1 g), b.p. 65–70°/0·2 mm, identified by infra-red spectroscopy.

Esterification of 5,5,5-*trifluorolaevulic acid* (II)

The acid (5·2 g), ethanol (10 ml) and sulphuric acid (3 ml, *d*, 1·84) were refluxed together for 6 hr. The reaction mixture was poured into water (50 ml) and, after the lower organic layer had been separated, the aqueous layer was extracted with ether (4 × 25 ml). The combined organic layers were dried ($MgSO_4$) and evaporated, and the residue was distilled *in vacuo* to give ethyl 5,5,5-trifluorolaevulate hydrate (VII, 3·0 g), b.p. 40–50°/0·2 mm, n_D^{28} 1·3689. Infra-red spectroscopy showed that this sample was identical with the sample from the hydrolysis of diethyl trifluoroacetosuccinate.

Treatment of 5,5,5-*trifluorolaevulic acid* (II) *with alkali*

The acid (0·5 g) was treated with an excess of 2 N sodium hydroxide. Effervescence occurred, the solution became warm and later turned purple. It was heated to 60°, allowed to cool, and kept at room temperature for 3 hr. Acidification with sulphuric acid followed by continuous ether extraction for 75 hr gave succinic acid (0·32 g), m.p. 185–187° (from water), unchanged on admixture with an authentic specimen (Found: equiv., 59. Calc. for $C_4H_6O_4$: equiv., 60).

Dehydration of 5,5,5-*trifluorolaevulic acid* (II)

(a) *With phosphoric oxide*. The acid (23 g) was refluxed with an excess of phosphoric oxide (6 g) for 2 min, and the crude product then distilled off: it was redistilled from fresh phosphoric oxide to give 4-*hydroxy*-5,5,5-*trifluoropent*-3-*enoic acid lactone* (III, 16·3 g), b.p. 180°, n_D^{23} 1·3831 (Found: C, 39·4; H, 2·3. $C_5H_5F_3O_2$ requires: C, 39·5; H, 2·0%) (Groth[3] quoted b.p. 170–172° and n_D^{20} 1·3853 for his product). Infra-red spectroscopy showed a carbonyl absorption at 1790 cm^{-1}, consistent[15] with $\beta\gamma$-unsaturation. Treatment of the lactone with alkali gave a deep purple colour: no tractable product could be obtained from this reaction. The compound had no maximum in the ultra-violet: the end absorption at 220 mμ had ε, approx 820 (in ethanol). The intensity fell steadily with increasing wavelength (ε, approx 60 at 260 mμ).

(b) *With sulphuric acid*. The acid (4·0 g) was refluxed with sulphuric acid (10 ml, *d*, 1·84) for 3 min. The cooled solution was poured into water (50 ml) and the product isolated by ether extraction (5 × 10 ml). It was the lactone (III, 2·0 g), b.p. 179–182°, n_D^{21} 1·3860, shown by infra-red spectroscopic analysis to be identical with specimen obtained in (a).

An attempted dehydration of the acid by azeotropic distillation with benzene was unsuccessful.

Reaction of ethyl 5,5,5-*trifluorolaevulate hydrate* (VII) *with phosphoric oxide*

The ester hydrate (5·2 g) was treated with an excess of phosphoric oxide as described for the parent acid [(a), above]. Infra-red spectroscopic analysis of the product showed that it was a mixture of 4-hydroxy-5,5,5-trifluoropent-3-enoic acid lactone (III, 60%) and ethyl 5,5,5-trifluorolaevulate hydrate (VII, 40%).

Acidic hydrolysis of the lactone (III)

The lactone (1·13 g) and sulphuric acid (25 ml, 5 N) were refluxed together for 6 hr. Isolation by ether extraction (4 × 10 ml) gave 5,5,5-trifluorolaevulic acid (II, 0·71 g), b.p. 65–71°/0·1 mm, identified by infra-red spectroscopic analysis.

[15] Reference 14, p. 179.

Reaction of the acid (II) *and the lactone* (III) *with carbonyl reagents*

(a) *2,4-Dinitrophenyl-hydrazine*. The acid (1·1 g) and 2,4-dinitrophenyl-hydrazine sulphate (1·1 g) were refluxed together for 1½ hr in ethanol containing 10% of water. Cooling gave a yellow precipitate of *1-(2′,4′-dinitrophenyl)-6-ethoxy-6-hydroxy-3-trifluoromethyl-1,4,5,6-tetrahydropyrazine* (IX, 0·5 g), m.p. 105·5–106° (from aqueous ethanol) (Found: C, 41·1; H, 3·5. $C_{13}H_{13}F_3N_4O_6$ requires: C, 41·3; H, 3·5%).

The same product (0·5 g), m.p. 105·5–106° (alone and on admixture with the specimen obtained from the acid) was obtained when the lactone (0·5 g) was treated in the same way.

The acid (0·5 g) reacted with 2,4-dinitrophenyl-hydrazine sulphate in 90% propanol to give *1-(2′,4′-dinitrophenyl)-6-hydroxy-6-propoxy-3-trifluoromethyl-1,4,5,6-tetrahydropyrazine* (X, 0·5 g), m.p. 62° (from aqueous propanol) (Found: C, 43·0; H, 3·9. $C_{14}H_{15}F_3N_4O_6$ requires: C, 42·9; H, 3·9%).

(b) *Hydroxylamine*. The acid (3·2 g), hydroxylamine hydrochloride (3·8 g), sodium acetate trihydrate (7·6 g) and water (30 ml) were refluxed together for 18 hr. Isolation by ether extraction (3 × 75 ml) gave a residue which was crystallized from benzene to give *5,5,5-trifluorolaevulic acid oxime* (XI, 1·3 g), m.p. 130–131° (Found: C, 32·8; H, 3·6. $C_5H_6F_3NO_3$ requires: C, 32·4; H, 3·3%).

The lactone (3 g) was treated with hydroxylamine hydrochloride (3·8 g) and sodium acetate trihydrate (7·6 g) in water (30 ml) in the same way to give the oxime (1·2 g), m.p. 129–130°, alone and on admixture with the specimen obtained from the acid.

Preparation of 5,5,5-trifluoropentane-1,4-diol (IV)

(a) *From 5,5,5-trifluorolaevulic acid* (II). The acid (25 g, 0·15 mole), dissolved in dry ether (100 ml), was added dropwise, with stirring, over a period of 1 hr to a solution of lithium aluminium hydride (10 g, 0·26 mole) in dry ether (250 ml). The mixture was refluxed, with stirring, for a further 3 hr, and then cautiously treated with water (100 ml), followed by sulphuric acid (300 ml, 20% v/v). The ether layer was separated and the aqueous layer extracted continuously with ether. Distillation of the dried ($MgSO_4$) extracts gave *5,5,5-trifluoropentane-1,4-diol* (IV, 18·5 g), b.p. 113–115°/12 mm, n_D^{20} 1·3921 (Found: C, 38·3; H, 5·6. $C_5H_9F_3O_2$ requires: C, 38·0; H, 5·7%).

The diol (1·2 g), on treatment with 3,5-dinitrobenzoyl chloride (2·1 g) in pyridine (25 ml), gave *5,5,5-trifluoropentane-1,4-diol bis-3′,5′-dinitrobenzoate* (2·3 g), m.p. 133–134° [from acetone–light petroleum (b.p. 60–80°)] (Found: C, 41·9; H, 2·5. $C_{19}H_{12}F_3N_4O_{12}$ requires: C, 41·8; H, 2·4%).

(b) *From the lactone* (III). The lactone (19·0 g, 0·125 mole) was reduced with lithium aluminium hydride (10 g, 0·26 mole) as described in (a) to give (i) the diol (IV, 10·7 g), b.p. 118–120°/14 mm, identified by infra-red spectroscopic analysis, and (ii) a higher-boiling fraction (2·6 g), b.p. 123–126°/0·3 mm, which has not been investigated further.

(c) *From ethyl 5,5,5-trifluorolaevulate hydrate*. The ester (3·0 g, 0·014 mole) was reduced with lithium aluminium hydride (1·34 g, 0·035 mole) as described in (a) to give the diol (IV, 1·65 g), b.p. 113–114°/12 mm, identified by infra-red spectroscopic analysis.

Acetylation of 5,5,5-trifluoropentane-1,4-diol (IV)

The diol (24·2 g), glacial acetic acid (100 ml) and acetic anhydride (100 ml) were refluxed together for 3 hr, then cooled and poured into water. After separation of the organic layer, the aqueous layer was extracted with ether (3 × 100 ml). The organic layers were combined and washed with a 10% aqueous solution of sodium bicarbonate. The washings were extracted with ether (2 × 50 ml) and the combined ethereal extracts were dried ($MgSO_4$) and concentrated to leave a residue which was distilled to give *5,5,5-trifluoropentane-1,4-diol diacetate* (V, 32·7 g), b.p. 210–212°, n_D^{20} 1·3890 (Found: C, 44·9; H, 5·0. $C_9H_{13}F_3O_4$ requires: C, 44·6; H, 5·4%).

Pyrolysis of 5,5,5-trifluoropentane-1,4-diol diacetate (V)

The pyrolysis apparatus, which consisted of a silica tube (28 cm × 1 cm diameter) packed with hard glass chips, was mounted vertically and surrounded by an electrically heated furnace. The diacetate (67 g) was introduced slowly into the heated (520 ± 5°) tube in a stream of nitrogen over a period of 100 min. The pyrolysis products were collected in cooled traps (at 0° and −78°), combined, and fractionally distilled through a 6″ long, vacuum-jacketed column packed with 1/16″ stainless steel Dixon gauzes to give 5,5,5-trifluoropenta-1,3-diene (VI, 25·3 g), b.p. 45–46°, n_D^{22} 1·3569

(Found: C, 49·4; H, 4·2. Calc. for $C_5H_5F_3$: C, 49·2; H, 4·1%) (cited[18] values: b.p. 45·2–45·9°, n_D^{20} 1·3571).

The diene (4·0 g) was treated overnight with an excess of bromine (4 ml) in glacial acetic acid (10 ml). The reaction mixture was poured into water (30 ml) and the lower layer was separated and distilled to give *dibromo-5,5,5-trifluoropentene* (8·0 g), b.p. 175°, n_D^{20} 1·4650 (Found: C, 21·5; H, 1·7. $C_5H_5Br_2F_3$ requires: C, 21·3; H, 1·8%). This product gave a single sharp peak in vapour phase chromatography (Didecyl phthalate/Kieselguhr, N_2 gas-stream) and its infra-red spectrum was also consistent with the presence of one isomer only. It had no strong absorption in the region 900–950 cm^{-1}.

Acknowledgements—We thank Professor M. Stacey, F.R.S., for his interest in this work, the Imperial Smelting Corporation for a scholarship (to T. J. S.) and the Department of Scientific and Industrial Research for a maintenance grant (to P. B.).

Tetrahedron, 1960, Vol. 10, pp. 171 to 174. Pergamon Press Ltd, Printed in Northern Ireland

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THE SIGNIFICANCE OF BENZENOID RINGS FOR THE STABILITY OF AROMATIC HYDROCARBONS

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(*Received* 7 *March* 1960)

Abstract—The hitherto unknown tribenzotetracene(V) was synthesized and fitted into the series: heptacene(I), benzohexacene(II), the dibenzopentacenes III and IV, tribenzotetracene(V) and tetrabenzanthracene (VI). It is obvious that in the series I → VI the stability increases and the absorption bands shift to shorter wavelength with the number of benzenoid rings (marked with circles). In contrast to this the absorption spectra of the benzotetracenes show little change in the annellation series VII → V → VIII because the benzenoid rings were fused to double bond which are already localized.

BENZENOID rings, i.e. rings which can be written with 3 double bonds and which are marked with circles, provide aromatic systems with additional stability.[1] They are also responsible for the localization of aromatic double bonds making these accessible

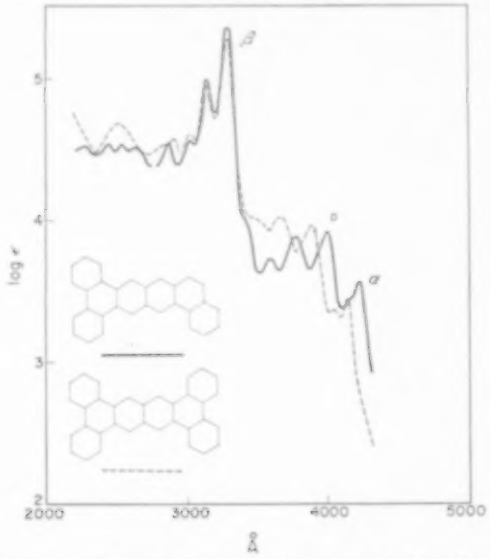

FIG. 1. Absorption max. (Å) and log ε (in parentheses). 1 :2,3 :4,7 :8-Tribenzotetracene V in benzene, α :4230 (3·56); p :4000 (3·92), 3780 (3·89), 3590 (3·73); β :3280 (5·36), 3130 (4·96), 3020 (4·56); 2870 (4·55); in cyclohexane, 2630 (4·50), 2530 (4·52), 2430 (4·52), 2270 (4·53). 1 :2,3 :4,7 :8,9 :10-Tetrabenzotetracene in benzene, α :4140 (3·50); p :3900 (3·98), 3680 (4·06); β :3280 (5·30), 3140 (4·90), 3010 (4·60), 2900 (4·58); in heptane, 2530 (4·68).

for the addition of maleic anhydride.[2] Benzenoid rings also explain the phenomenon of assymetric annellation.[3]

In the series of the isomeric hydrocarbons $C_{30}H_{18}$ I → VI, there is an increase in the

[1] T. W. Armit and R. Robinson, *J. Chem. Soc.* 1604 (1925); E. Clar, *Tetrahedron* **5**, 98 (1959); **6**, 355 (1959).
[2] E. Clar, C. T. Ironside and M. Zander, *Tetrahedron* **6**, 358 (1959).
[3] E. Clar, *Tetrahedron* **5**, 98 (1959); **6**, 355 (1959); **9**, 202 (1960).

number of benzenoid rings to the maximum in the fully benzenoid tetrabenzanthracene(VI). Heptacene(I) is a green, most reactive hydrocarbon, which cannot be obtained in a pure state because of its reactivity.[4] It has only one benzenoid ring which is shared among seven rings. 1:2-Benzohexacene(II) is blue-green and because of its two benzenoid rings, somewhat more stable. However, a complete absorption spectrum has not yet been obtained, only the *p*-bands were measured by visual observation.[5] The two dibenzopentacenes III and IV, both having three benzenoid rings are very similar and considerably more stable than pentacene.[6] The small

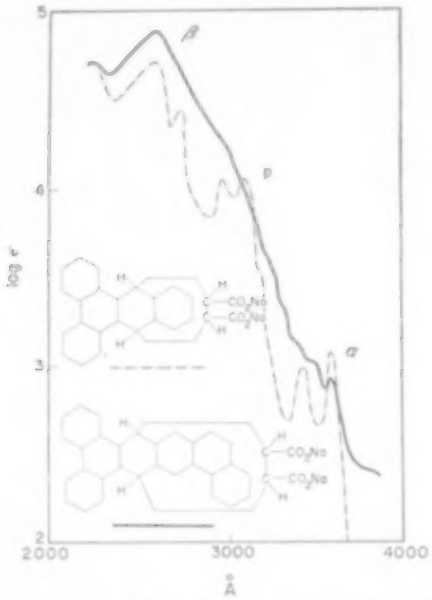

FIG. 2. Absorption max (Å) and log ε (in parentheses). Disodium salt derived from X in water, p:3580 (2·92); β:2610 (4·89). Disodium salt of the adduct of 1:2,3:4-dibenzanthracene and maleic anhydride [E. Clar, *Ber. Dtsch. Chem. Ges.* **65**, 507 (1932)] in water, α:3590 (3·08), 3420 (2·98); p:3100 (4·06), 2·980 (4·05), 2740 (4·44); β:2600 (4·70).

differences between III and IV might be explained by the different relative positions which the benzenoid rings can assume. The hitherto unknown tribenzotetracene(V) is yellow and reacts more slowly with maleic anhydride than most benzotetracenes, except tetrabenzotetracene(VIII).[3] The colourless tetrabenzanthracene(VI)[7] does not react with maleic anhydride. Its absorption spectrum is the most shifted to the short wave among its isomers. Thus tribenzotetracene(V) fits perfectly into the series predicted by the assumption of benzenoid rings within the aromatic system.

If 1:2,7:8-dibenzotetracene(VII) is given the maximum number of benzenoid rings, the two terminal double bonds in the central tetracene system appear to be fixed. Accordingly, annellation to these double bonds produces only a small shift of the β-bands in passing to tribenzotetracene(V) and tetrabenzotetracene(VIII). The red

[4] B. Boggiano and E. Clar, *J. Chem. Soc.* 2683 (1957).
[5] E. Clar, and Ch. Marschalk, *Bull. Soc. Chim.* 444 (1950).
[6] E. Clar, *Ber. Dtsch. Chem. Ges.* **76**, 257 (1943); E. Clar and H. Frömmel, *Chem. Ber.* **81**, 163 (1948).
[7] P. Lambert and H. Martin, *Bull. Soc. Chim. Belg.* **61**, 124 (1952).

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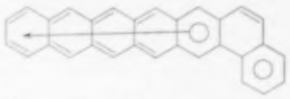
dark green

I



blue green

$\lambda p = 6510$

II

-2980

red

$\lambda p = 5230$

$\lambda\beta = 3470$

III

$+155$

-40

violet red

IV

$= 5385$ Å

$= 3430$ Å

-1385

-150

yellow

$\lambda\sigma = 4250$

$\lambda p = 4000$

$\lambda\beta = 3280$

V

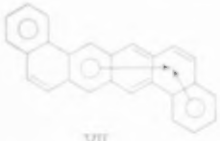
-450 → 3820 Å

-665 → 3335 Å

-330 → 2950 Å

colourless

VI



VII

$\lambda\sigma =$ ——

$\lambda p = 4375$

$\lambda\beta = 3255$

-375

$+25$

V

4250

4000

3280

-110

-100

0

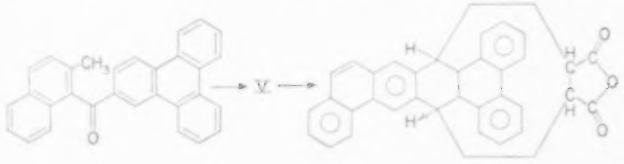
VIII

4140 Å

3900 Å

3280 Å

All wavelengths were measured in benzene except II which is in 1-methylnaphthalene



IX X

shift, due to the addition of the 4π-electrons per ring, is compensated by the violet shift, due to the formation of a new aromatic sextet.[8] The movement of the sextet through the central tetracene system is not restricted in the series VII, V and VIII in contrast to the increasing restriction imposed in the series I → VI as indicated by the arrows.

Tribenzotetracene was obtained by pyrolysis of the ketone IX which was prepared from 2-methyl-1-naphthoyl chloride, triphenylene and aluminium chloride. The reaction proceeded analogous to the condensation of triphenylene[9] with other acid chlorides which gave only substitution in the β-positions. However, another condensation product which does not react with maleic anhydride was observed in the pyrolysis. The adduct of maleic anhydride with tribenzotetracene(X) showed an absorption spectrum (Fig. 2) which indicated the presence of a 9,10-substituted phenanthrene complex. Therefore the addition must have taken place in position 5 and 12. The adduct was readily decomposed by sublimation with soda lime and yielded pure tribenzotetracene (V).

EXPERIMENTAL*

2-Methyl-1-naphthoyl-2′-triphenylenyl-ketone(IX). To triphenylene (7 g) and 2-methyl-1-naphthoyl chloride[10] (7 g) in chlorobenzene (20 ml) or in benzene (50 ml) powdered aluminium chloride (12 g) was added. After a slight warming the reaction began and the triphenylene went into solution. The dark reddish-yellow mixture was heated to 50° for a few min until the evolution of HCl ceased. After decomposition with dil HCl the solvent was removed by steam distillation. The resinous residue crystallized when treated with ether. The *ketone*(IX) was recrystallized first from xylene and then from acetic acid. It formed very pale yellow needles, m.p. 214–216°, which dissolved in conc H_2SO_4 forming a red solution. (Found: C, 90·6; H, 4·9. $C_{30}H_{20}O$ requires: C, 90·9, H, 5·1%).

1:2,3:4,7:8-*Tribenzotetracene*(V). The ketone (10 g) was heated to 400–420° under the protection of a current of carbon dioxide. The formation of water was completed after ½ hr. The residue was sublimed at 270°/1 mm. Triphenylene (0·77 g) was first obtained, followed by the yellow hydrocarbon at 350°/1 mm. The crude hydrocarbon was recrystallized from xylene and was found not to be uniform (1·97 g). For further purification it was transformed into the adduct X with boiling maleic anhydride. The excess of maleic anhydride was removed with boiling water and the residue several times extracted with sodium hydroxide in aqueous alcoholic solution. This left a colourless by-product undissolved which was filtered off. The united filtrates were acidified with HCl and the white precipitate (1·1 g) washed with water and dried.

The adduct was mixed with soda lime (1·5 g) and sublimed at 300°/0·1 mm. The *tribenzotetracene* which formed yellow needles was repeatedly recrystallized from xylene. When the solution was quickly cooled it yielded yellow wart-like conglomerates and on slow crystallization long needles. The hydrocarbon dissolved in conc H_2SO_4 with a blue colour (absorption band about 6200 Å) which soon changed to green and then to yellow. Both forms have m.p. 277–278°. (Found: C, 95·3; H, 4·5. $C_{26}H_{16}$ requires: C, 95·2; H, 4·8%).

1:2,3:4,7:8-*Tribenzotetracene-maleic anhydride adduct*(X). This adduct was obtained by boiling pure tribenzotetracene with excess maleic anhydride. After removing the excess maleic anhydride the adduct was dissolved in aqueous-alcoholic sodium hydroxide filtered and the *free acid* precipitated with HCl. It formed a white powder which decomposed at 190–192°. (Found: C, 82·6; H, 4·8. $C_{34}H_{22}O_4$ requires: C, 82·6; H, 4·5%).

* Melting points are uncorrected and were taken in evacuated capillaries. Microanalyses by J. M. L. Cameron and his staff, Glasgow University.

[8] E. Clar, *Tetrahedron* in press.
[9] E. Clar, *Chem. Ber.* **81**, 68 (1948); *J. Chem. Soc.* 2440 (1949).
[10] R. Adams and L. O. Binder, *J. Amer. Chem. Soc.* **63**, 2774 (1941).

Tetrahedron, 1960, Vol. 10, pp. 175 to 181. Pergamon Press Ltd. Printed in Northern Ireland

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STUDIES ON THE SYNTHESES OF HYDROGENATED QUINOLINES AND ISOQUINOLINES AS ANALGESICS—XVIII[1]

SYNTHESIS OF 3-HYDROXY-N-METHYL-8-AZA-DES-N-MORPHINAN. (4-METHYL-9-HYDROXY-5·10b-TRIMETHYLENE-1,2,3,4,4a,5,6,10b-OCTAHYDROBENZO [F] QUINOLINE)

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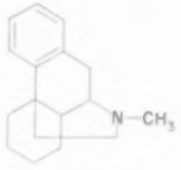
(*Received* 22 *March* 1960)

Abstract—The introduction of a hydroxy group into N-methyl-8-aza-des-N-morphinan at the 3-position was achieved through nitration of the parent compound, followed by reduction and diazocization. The position of the substituent was determined by the spectral evidence from 3-methoxy-10-oxo-8-aza-des-N-morphinan which was derived from 3-hydroxy-8-aza-des-N-morphinan via the oxidation of 3-methoxy-derivative. A pharmacological study of the compound is also presented.

IT is a well known fact that the introduction of a hydroxy group into N-methylmorphinan at the 3-position produces a marked increase in its analgesic properties.[2]

With respect to this fact, Sugimoto *et al.* have introduced the hydroxy group at the 3-position of their N-shifted morphinan isomers, e.g. 9, 15, 16, 6 and 7-aza-des-N-morphinan for possible pharmacological benefits.[3]

The present author reports consecutively the introduction of a hydroxy group into



N—methyl—morphinan

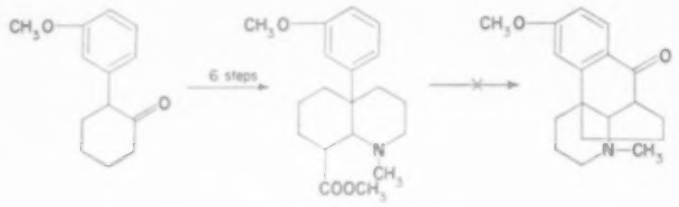
des—N—morphinan

N-methyl-8-aza-des-N-morphinan and the pharmacological testing of the resulting 3-hydroxy compounds.

Sugimoto and the present author reported the synthesis of a preliminary compound, N-methyl-8-aza-des-N-morphinan, starting with 2-phenylcyclohexanone. In the present study 2-(*m*-methoxyphenyl)-cyclohexanone(I) was utilized as the starting material and 1-methyl-8-methoxycarbonyl-10-(*m*-methoxyphenyl)-decahydroquinoline(II) was synthesized by a route analogous to that used for the corresponding desmethoxy compound. After the hydroxylis of the methyl ester ring closure of the resulting carboxy compound with polyphosphoric acid was attempted. Intractable

[1] Part XVII: S. Ohshiro, *Tetrahedron* **8**, 304 (1960).
[2] O. Schneider and A. Grüssner, *Helv. Chim. Acta* **32**, 821 (1949); O. Schneider and J. Hellerbach *Ibid.* **33**, 1437 (1950).
[3] N. Sugimoto and H. Kugita, *Pharm. Bull. Tokyo* **3**, 11 (1955); E. Ochiai and K. Harasawa, *J. Pharm. Soc. Japan* **77**, 168, 172 (1957); N. Sugimoto and S. Ohshiro, *Pharm. Bull. Tokyo* **4**, 357 (1956); N. Sugimoto and S. Ohshiro, *Ibid.* **5**, 316 (1957); N. Sugimoto and H. Kugita, *Ibid.* **6**, 427 (1958).

material resulted instead of the ketonic compound III probably due to the production of phenolic material by the demethylation that would take place during the reaction. No further attempt of ring closure has been conducted.

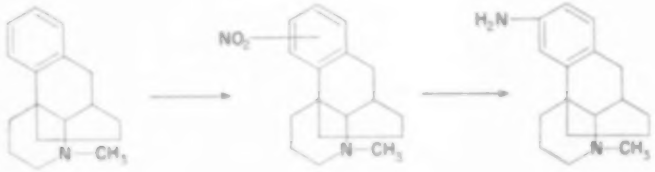


I II III

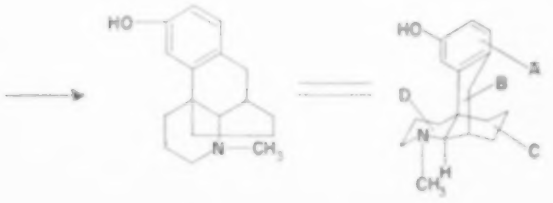
The most feasible alternative approach to the title compound appeared to be through the nitration of N-methyl-8-aza-des-N-morphinan(IV).[1] Nitration[2,4] of IV in acetic acid with fuming nitric acid gave a mixture of two isomers, from which an isomer Va separated slowly, on standing, as pale yellow crystals m.p. 94–96° in a yield of 57 per cent. The rest was converted to picrate; repeated recrystallizations finally gave two pure picrates of m.p. 227–229° and 221–223°. The higher-melting picrate gave the free base Va m.p. 94–96°, while an isomer of the free base Vb m.p. 83–85° in a poor yield, was obtained from the other. These two bases were proved by their analytical values and I.R. spectra to be isomeric with respect to the position at which the nitro group was attached.

It can be assumed that the nitration of this type of compound would take place at the 2 and/or 3 positions and it is probably the case in the present study that the 3-position would be favoured due to less steric hindrance and the reactivity which is induced by hyperconjugation at the *p*-position.

From the above considerations the nitro compound of higher yield was tentatively designated as 3-nitro-N-methyl-8-aza-des-N-morphinan and used for the further



IV Va Vb VI



VII

[4] M. Gates and W. G. Webb, *J. Amer. Chem. Soc.* **80**, 1186 (1958).

studies, while the other product of lower yield—not more than 5 per cent yield—as 2-nitro-8-aza-des-N-morphinan, which consistently showed the out-of-plane vibration of a 1,3,4-trisubstituted benzene in its I.R. spectrum.

The 3-nitro compound (Va) was reduced catalytically to the 3-amino compound (VI) from which 3-hydroxy-8-aza-N-morphinan was obtained through the intermediate diazo compound. The 3-hydroxy compound(VII) is soluble in alkali hydroxide- and insoluble in alkali carbonate and with ferric chloride it gave an orange-yellow colour. The I.R. spectrum is presented in Fig. 1.

VII was converted to the 3-methoxy compound(VIII) by the action of diazo-

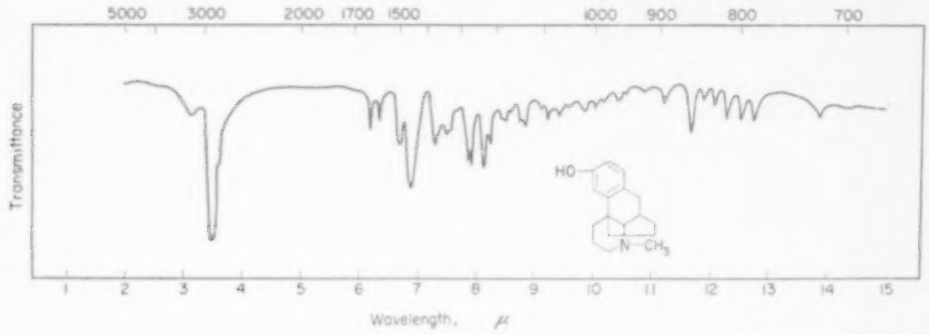


FIG. 1.

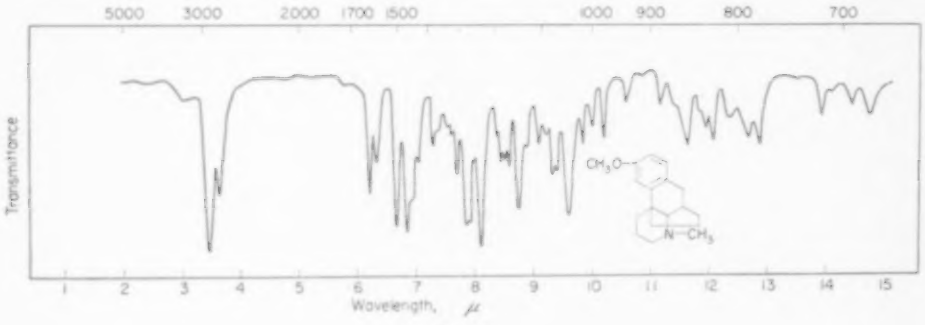


FIG. 2.

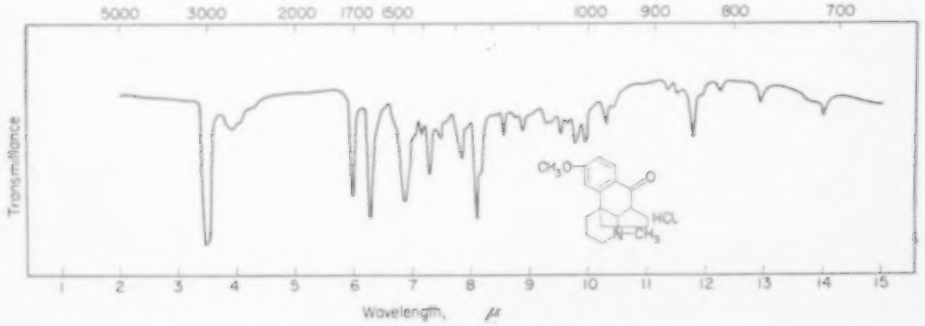
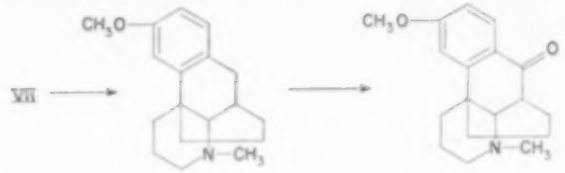


FIG. 3.

methane. Chromic acid oxidation[5] of VIII furnished the 10-oxo-compound IX. The presence of a carbonyl group in IX at the 10-position was clearly indicated by the spectral evidence; The I.R. spectrum (Fig. 3) has a strong band at 1680 cm^{-1} characteristic of aryl ketones.



VIII IX

The comparison of the U.V. spectra (Fig. 5) of 6-methoxy and 7-methoxy-α-tetralone with that of the present methoxy compound appeared to provide most valuable information supporting structure IX for the methoxy compound. There is some

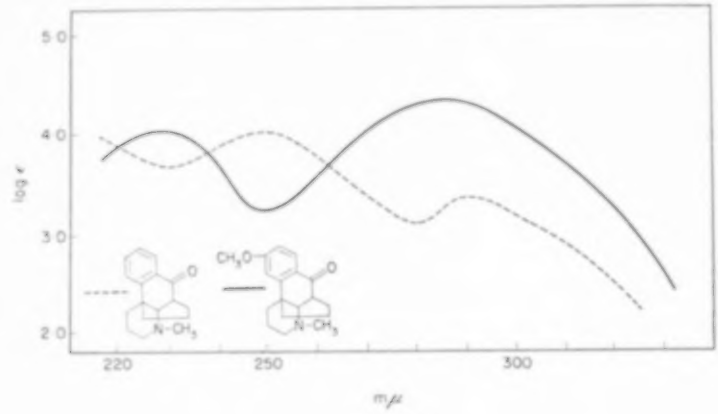


FIG. 4.

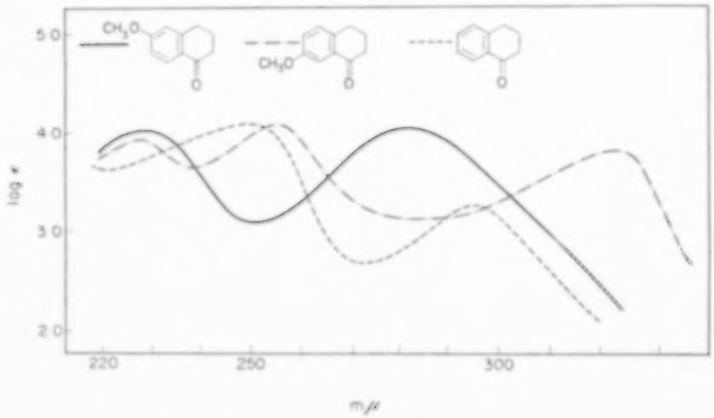


FIG. 5.

[5] O. Schneider, M. Walter and A. Brossi, *Helv. Chim. Acta* **39**, 2053 (1956).

relationships between α-tetralone and methoxy-substituted α-tetralones in their U.V. spectra.[6,7]

(1) Introduction of a methoxy group at the 5 or 7-position of α-tetralone produces a marked bathochromic shift from 293 mμ to 325 mμ of its first band, but does not change the second band at 248 mμ. (2). Introduction of a methoxy group at the 6-position of α-tetralone leaves its first band unchanged, contrary to the above observation, while it shifts the second band bathochromically from its normal position to 277 mμ, so that it falls almost on the first band. As can be seen in Fig. 4 this same relation can be found between the U.V. spectrum of N-methyl-10-oxo-8-aza-des-N-morphinan and that of the methoxy derivative(IX). It is therefore most likely that the present methoxy derivative is 3-methoxy-10-oxo-8-aza-des-N-morphinan(IX) and consequently the nitro compound (Va) is 3-nitro-8-aza-des-N-morphinan.

As for the stereochemical nature of 3-hydroxy-N-methyl-8-aza-N-morphinan (VII) it can be safely concluded that the compound has the same ring configuration (B/c:*cis*) as that of starting material, N-methyl-8-aza-des-N-morphinan which was proved to be the same as morphine in its ring structure.

Pharmacological tests of the compound VII were made by Dr. H. Fujimura in the Pharmacological Department, University of Kyoto, for analgesic activity in mice. Its toxicity was 0·79 mg/10 g by intraperitoneal injection, showing it to be somewhat stronger than that of codeine. Analgesic action measured by the Haffner, D'Amour-Smith method, and inhibiting effect of stretching gave the following results.

	Compound (VII)	Codeine phosphate
Haffner method	ED_{50} 0·38 mg/10 g	ED_{50} 0·50 mg/10 g
D'Amour-Smith method	ED_{50} 0·19 mg/10 g	ED_{50} 0·178 mg/10 g
Inhibiting effect of stretching	ED_{50} 0·044 mg/10 g	ED_{50} 0·048 mg/10 g

Accordingly, VII showed analgesic action about equal to that of codeine. Antitussive action was determined by Dr. Y. Kasé of the Pharmaceutical Department, University of Kumamoto, by the Kasé method,[8] using a dog and a cat.

A value of minimal antitussive dose was 2·5 mg/kg (dog) and 2·12 mg/kg (cat), while that of control codeinephosphate was 3·76 mg/kg and 2·53 mg/kg, respectively, showing VII to be somewhat stronger than codeinephosphate.

EXPERIMENTAL

3-Nitro-N-methyl-8-aza-des-N-morphinan (Va). A solution of IV (1·5 g) in glacial acetic acid (5 cc) was added dropwise with stirring to the solution of fuming nitric acid (d = 1·52, 7·5 cc) in glacial acetic acid (4·4 cc), cooled to 3° during 1½ hr, at a temp below 5°. The reaction mixture was allowed

[6] T. Momose, Y. Ohkura and S. Goya, *Pharm. Bull. Tokyo* **3**, 401 (1955).
[7] K. Miki, *J. Pharm. Soc. Japan* **61**, 272 (1941).
[8] Y. Kasé, *Pharm. Bull. Tokyo* **2**, 298 (1954); *Japan. J. Pharm.* **4**, 130 (1955).

to stand overnight at room temp and then acetic acid was removed under reduced pressure and temperature not exceeding 60°.

The residue was diluted with ice water, basified with aqueous ammonia, and the separated base extracted with ether. On evaporating the washed and dried ethereal solution a viscous pale yellow oil was obtained. This oil was purified by vacuum distillation yielding b.p. 135–140°/0·3 mm (original substance, 0·2 g), and b.p. 170–180°/0·3 mm, a mixture of Va and Vb (1·3 g). The higher boiling product was dissolved in pet ether (10 cc), and allowed to stand overnight at 0° with separation of pale yellow crystals. The crude product was recrystallized from pet ether to yield Va (1·02 g 57%) as pale yellow rods, m.p. 96–97°.

(Found: C, 71·3; H, 7·74; N, 9·78. $C_{17}H_{22}N_2D_2$ requires: C, 71·5; H, 7·7; N, 9·2%).

Picrate: Yellow plates (from acetic acid), m.p. 227–229°.

(Found: C, 53·59; H, 4·89; N, 13·59. $C_{23}H_{25}N_5O_9$ requires: C, 53·8; H, 4·8; N, 13·6%).

2-*(or* 4)-*Nitro*-N-*methyl*-8-*aza*-*des*-N-*morphinan* (Vb). A solution of picric acid in acetone was added to the mother liquor obtained by filtration of Va and the resulting mixture was allowed to stand overnight at 0°.

The separated picrate was filtered, and then washed with ethanol, and recrystallized from acetic acid to give yellow plates, m.p. 226–228° and identified as Va picrate by a mixed m.p.

The filtrate from the Va-picrate was concentrated until the appearance of Vb-picrate, which was collected, and recrystallized from acetone–ethanol. Vb-picrate m.p. 221–223° showed by mixed m.p. determination with Va-picrate a depression of about 10°.

The free base of Vb-picrate was recrystallized from pet ether to give pale yellow columns, m.p. 83–85°, but yielded only 5% Vb and was depressed by mixed m.p. with Va.

(Found: C, 71·3; H, 7·74; N, 9·78. $C_{17}H_{22}N_2O_2$ requires: C, 70·4; H, 7·00; N, 9·63%).

3-*Amino*-N-*methy*-8-*aza*-*des*-N-*morphinan*(VI). A solution of Va (0·2 g) in ethanol (15 cc) was hydrogenated at atmospheric pressure in the presence of 15% Pd-C (0·2 g as the catalyst. Three equivalents of hydrogen were absorbed in 30 min, and further absorption was very slow. The filtrate from the catalyst was concentrated to about 3 cc, cooled and the separated crystals purified from ethanol giving VI (0·15 g 84%) as colourless needles, m.p. 210–212°. The diazo test was positive in acidic solution.

Found: C, 79·64; H, 9·44; N, 10·49. $C_{17}H_{24}N_2$ requires: C, 79·7; H, 9·3; N, 10·25%).

3-*Hydroxy*-N-*methyl*-8-*aza*-*des*-N-*morphinan*(VII). A solution of VI (1·3 g) in 3-N-sulphuric acid was cooled to 3° and treated dropwise with vigorous stirring for 10 min with a solution of sodium nitrite (0·43 g) in water (5 cc). The reaction mixture was maintained at this temperature for 30 min, and then added at once with stirring to 50% sulphuric acid (56 cc) at 70°. The mixture was then heated at 85° for 30 min, cooled, and basified with aqueous ammonia. The semi-solid substance was extracted with ether, and the ethereal solution extracted with 10% aqueous sodium hydroxide. The aqueous layer was washed with ether, and treated with solid sodium bicarbonate. The precipitated solid was extracted with ether, washed and dried. The residue was recrystallized from methanol (with charcoal and VII (1·1 g 84%) was obtained as a colourless columns, m.p. 204–205°.

(Found: C, 79·33; H, 9·01; N, 5·44. $C_{17}H_{22}NO$ requires: C, 79·6; H, 8·7; N, 5·25%).

Hydrochloride: Colourless plates (from methanol–ether), m.p. 279° (dec).

(Found: C, 65·6; H, 8·35; N, 4·50. $C_{17}H_{24}NO\,Cl{\cdot}H_2O$ requires: C, 65·1; H, 8·1; N, 4·54%).

Picrate: Yellow granulars (from methanol), m.p. 214–216°.

(Found: C, 56·78; H, 5·39; N, 11·52. $C_{23}H_{26}N_4O$- requires: C, 56·35; H, 5·05; N, 11·44%)

3-*Methoxy*-N-*methyl*-8-*aza*-*des*-N-*morphinan*-(VIII). Excess of ethereal diazomethane was added to a suspension of VII (0·35 g) in methanol (10 cc) and the mixture was allowed to stand for 3 days a room temp. After evaporation of the solvent, the residue was distilled *in vacuo*, giving VIII (0·35 g) as a viscous pale yellow oil, b.p. 175–180° (bath temp.) /0·3 mm.

Picrate: Yellow columns (from ethanol), m.p. 196·5–198·5°.

(Found: C, 57·59; H, 5·64; N, 11·29. $C_{24}H_{25}N_4O_8$ requires: C, 57·3; H, 5·25; N, 11·3%).

3-*Methoxy*-10-*oxo*-N-*methyl*-8-*aza*-*des*-N-*morphinan*(IX). A mixture of VIII (100 mg), chromium trioxide (45 mg) in N-sulphuric acid (18 cc) was treated dropwise with stirring at room temperature for a period of 3 hr with 10-N-sulphuric acid (2 cc). The reaction mixture, which gradually changed from orange to green was allowed to stand overnight at room temp. The mixture basified with aqueous ammonia, extracted with ether, washed with water, dried and acidified to congo red with ethanolic hydrogen chloride, was allowed to stand for 5 hr at 0°.

The separated crystalline IX-hydrochloride was collected and recrystallized from ethanol–ether, giving 50 mg of colourless needles, m.p. 250° (dec).

(Found: C, 67·18; H, 7·46; N, 4·35. $C_{18}H_{21}NO_2Cl$ requires: C, 67·25; H, 7·45; N, 4·00%).

Picrate: Yellow granules (from acetone), m.p. 251° (dec).

(Found: C, 56·03; H, 5·09; N, 10·89. $C_{24}H_{26}N_4O_9$ requires: C, 56·00; H, 5·15; N, 10·3%).

Acknowledgements—The author is indebted to Messrs. K. Kodera and K. Furusaki for infra-red and ultra-violet spectral measurements, and to Mrs. F. Hisamichi and Messrs. T. Yoda and T. Kawano for elemental analyses reported herein.

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Tetrahedron, 1960, Vol. 10, pp. 182 to 199. Pergamon Press Ltd. Printed in Northern Ireland

THE NATURE OF THE STRUCTURE DIFFERENCE BETWEEN LIGHT AND HEAVY WATER AND THE ORIGIN OF THE SOLVENT ISOTOPE EFFECT[1-3]—I

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(*Received* 19 *October* 1959; *in revised form* 28 *March* 1960)

Abstract—The observed differences in heat content, entropy and free energy of light and heavy liquid water can be calculated within experimental error from measured infrared frequencies, using a model for water with tetrahedral hydrogen bonding and treating the hindered rotations (librations) of the water molecules as three-dimensional isotropic harmonic oscillators. The origin of the solvent isotope effect for monatomic ions in light and heavy water is their effect on the structure difference between light and heavy water. The quantity $\Delta\theta = h\,\Delta\nu/k$ provides a measure of this structure difference, where $\Delta\nu$ is $\nu - \nu'$, the difference in average values of the librational frequencies of H_2O and D_2O, and $\nu' = \nu/1{\cdot}3815$. Differences in heat content, entropy and free energy for solution of monatomic ions in light and heavy water and individual ionic activity coefficients can be calculated from $\Delta\theta$. Hydronium and hydroxide ions are also discussed.

"SOLVENT isotope effect" is a term frequently used in discussions of kinetic and equilibrium processes in light and heavy water for the part of the total isotope effect which is attributed to isotopic substitution of the solvent. Solvent isotope effects are of increasing concern to organic chemists studying reaction mechanisms *via* isotope effects. They have been said to be due primarily to differences in structure of the two waters.[4-6] However, no indication was given as to the cause of the structure of either solvent alone, nor any reasons proffered as to why there should be differences in structure. That differences do exist is evident from differences in thermodynamic properties of the two liquids,[7-9] and in heats of hydration[10] and solubilities[4,11] of salts in the two waters.

La Mer[12-16] and Noonan[17], who determined a number of exchange constants for processes conducted in the two media, stressed that these equilibrium measurements unfortunately lump together free energies of both exchange and transfer.

[1] Supported in part by the Atomic Energy Commission Under Contract No. AT(30-1)-905 and by the National Institutes of Health under Research Grant RG-3711(C4).
[2] *Cf.* Part II: C. G. Swain, R. F. W. Bader and E. R. Thornton *Tetrahedron*, **10**, 200 (1960).
[3] For further details, *cf.* R. F. W. Bader, Ph.D. Thesis in Organic Chemistry, M.I.T., December, 1957.
[4] R. W. Shearman and A. W. C. Menzies, *J. Amer. Chem. Soc.* **59**, 185 (1937).
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[6] P. M. Laughton and R. E. Robertson, *Canad. J. Chem.* **34**, 1714 (1956); R. E. Robertson, *Ibid.* **35**, 613 (1957); R. E. Robertson and P. M. Laughton, *Ibid.* **35**, 1319 (1957).
[7] E. A. Long and J. D. Kemp, *J. Amer. Chem. Soc.* **58**, 1829 (1936).
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[10] E. Lange and W. Martin, *Z. Physik. Chem.* **A180**, 233 (1937).
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[12] S. Korman and V. K. La Mer, *J. Amer. Chem. Soc.* **58**, 1396 (1936).
[13] C. K. Rule and V. K. La Mer, *J. Amer. Chem. Soc.* **60**, 1974 (1938).
[14] E. C. Noonan and V. K. La Mer, *J. Phys. Chem.* **43**, 247 (1939).
[15] F. Brescia, V. K. La Mer and F. C. Nachod, *J. Amer. Chem. Soc.* **62**, 614 (1940).
[16] R. W. Kingerly and V. K. La Mer, *J. Amer. Chem. Soc.* **63**, 3256 (1941).
[17] E. C. Noonan, *J. Amer. Chem. Soc.* **71**, 102 (1949).

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Similarly, the understanding of kinetic isotope effects for reactions involving hydroxide ion in light and heavy water[18] is hampered by difficulty in unraveling the solvent isotope effect from the effect due to the difference between the reactants HO^- and DO^-.

Calculation of thermodynamic differences for light and heavy water

Model for liquid water. Our working model is essentially that of Bernal and Fowler[19]. From a consideration of spectral and X-ray data they proposed structures in which each molecule is tetrahedrally bonded to exactly four others as illustrated in Fig. 1. Hydrogen-bonding with this geometry is not possible for other molecular liquids.

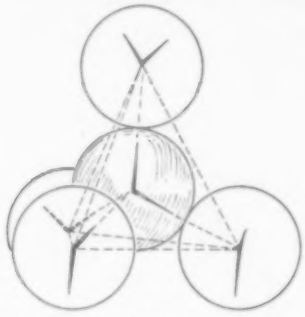

FIG. 1. Structural element of liquid water.

With this model they were able to deduce many of the physical properties of water and ice quantitatively in good agreement with experiment. They also concluded that the dielectric constants of water and ice and their variation with temperature and frequency are explicable only if most of the water molecules are not able to undergo free rotation, and hence not free to respond to an externally applied electric field. The dipole interaction pictured in Fig. 1 thus hinders rotation of the water molecules. Pople[20] quantitatively accounted for the X-ray radial distribution function, the discontinuity in density associated with the melting of ice, and the observed values of the dielectric constant of water, also by using four hydrogen bonds to nearest neighbors and considering the hindered rotation as bond bending. The essential difference between ice and water is that in ice the four bonds from one molecule bend only in such a way that the lattice order is retained, while in water they bend independently. The bond bending in Pople's theory and its associated force constant may be related to the hindered rotation and librational frequency of the present paper. The tetrahedron is not regular because the kinetic energy of the librations (hindered rotations) gives a resultant average OHO angle of less than 180°. Actually the calculations below for H_2O and D_2O do not even require the assumption of four coordination. However, we assume a tetrahedral model for clarity in discussing the kinds of motions involved because the evidence for it is so compelling.

Bernal and Tamm[21] calculated that the librational motion (hindered rotation)

[18] W. E. Nelson and J. A. V. Butler, *J. Chem. Soc.* 957 (1938); S. H. Maron and V. K. La Mer, *J. Amer. Chem. Soc.* **60**, 2588 (1938).

[19] J. D. Bernal and R. H. Fowler, *J. Chem. Phys.* **1**, 515 (1933); *cf.* J. W. Ellis, *Phys. Rev.* **38**, 693 (1931); S. Katzoff, *J. Chem. Phys.* **2**, 841 (1934); J. Morgan and B. E. Warren, *Ibid.* **6**, 666 (1938); G. W. Brady and W. J. Romanow, *Ibid.* **32**, 306 (1960).

[20] J. Lennard-Jones and J. A. Pople, *Proc. Roy. Soc.* A **205**, 155 (1951); J. A. Pople, *Ibid.* A **205**, 163 (1951).

[21] J. D. Bernal and G. Tamm, *Nature, Lond.* **135**, 229 (1935).

contributes about 17 per cent to the difference in heat content between light and heavy ice. They stated that a difference of comparable magnitude, again due to libration, should exist between light and heavy water, and that this difference would be affected by added ions. The librational motion clearly plays an important role in determining the differences in thermodynamic properties of H_2O and D_2O. We will show that it plays the predominant role in determining solvent isotope effects.

Calculations for H_2O *and* D_2O. We will first calculate the thermodynamic differences between light and heavy water by treating the librational motion of each water molecule as a three-dimensional isotropic harmonic oscillator. This approximate treatment of the hindered rotation may be justified as follows. Pitzer and Gwinn[22] showed that the quantum partition function for a hindered rotor can be well approximated by $Q_r = Q_{\text{class}} Q_q / Q_c$ where Q_{class} is the classical partition function for translation and rotation and Q_q and Q_c are the quantum and classical partition functions for a harmonic oscillator. In the case of isotopic molecules with no translational motion, the ratio Q_r'/Q_r reduces to Q_q'/Q_q, and Stockmayer[23] has demonstrated that for a system of nearly classical rotors the difference in heat capacities for isotopic hindered rotors will agree with that predicted from the harmonic oscillator approximation as long as the barrier is comparable to or greater than kT. Blue[24] showed that the observed differences in the heat capacities of solid H_2O and D_2O can be accounted for in the above manner.

The barrier to free rotation of the water molecules in liquid water at 25° is considerably greater than kT since it gives rise to a vibration with an average frequency of 667 cm^{-1}. The water molecule is an asymmetric top and thus possesses three different principal moments of inertia. However, only one broad band with one maximum is observed due to the thermal motions of the molecule. Accordingly we will use an *average librational frequency*. Although we will see below that the use of the observed maximum for this average frequency for light water with no adjustable parameter actually does give good agreement of calculated and observed thermodynamic quantities, there is no *a priori* reason to expect or require agreement of this average frequency with any observed frequency. The average librational frequency could have been used as an adjustable parameter in our theory, although in fact it was not.

The three librational isotopic frequency ratios should equal the inverse ratios of the corresponding moments of inertia to the one-half power. We employ, as did Blue[24], the mean of the three ratios to calculate the isotopic shift in the librational frequency, since none of the three ratios differs by more than 5·8 per cent from the mean. Thus the librational frequency ratio ω_r/ω_r' is $(1{\cdot}9083)^{1/2}$ or 1·3815, and this is the isotopic shift which should be employed in calculations using the harmonic oscillator approximation.[25] There is a close correspondence between this value and the observed value of 1·35 in Table 1, which lists the librational frequencies observed for water and ice at various temperatures. For the librational frequency the observed value of ω_r (Table 1) was used, but ω_r' for heavy water was taken as $\omega_r/1{\cdot}3815$.

Since rotation and translation are inextricably bound together, Q_{class} of the Pitzer–Gwinn approximation will involve both the rotational and translational degrees of freedom.[3] Since light and heavy water form nearly ideal solutions[25] the configurational

[22] K. S. Pitzer and W. D. Gwinn, *J. Chem. Phys.* **10**, 428 (1942); K. S. Pitzer, *Ibid.* **14**, 239 (1946); J. E. Kilpatrick and K. S. Pitzer, *Ibid.* **17**, 1064 (1949).
[23] W. H. Stockmayer, *J. Chem. Phys.* **27**, 321 (1957).
[24] R. W. Blue, *J. Chem. Phys.* **22**, 280 (1954).
[25] I. Kirshenbaum, *Physical Properties and Analysis of Heavy Water*. McGraw-Hill, New York (1951).

integrals contained in Q_{class} may be equated. The result is that the external degrees of freedom contribute the factor $(Q_q'/Q_q)(M'/M)^{3/2}$ to the total partition function ratio Q'/Q where primes denote the heavier molecule and M is molecular weight. The hindered translations are of such low frequency (approximately 170 cm^{-1})[26] that this classical treatment of them is justifiable.

TABLE 1. LIBRATIONAL FREQUENCY OF WATER AND ICE[a]

T, °C	ω_r, cm^{-1}	ω_r', cm^{-1}	ω_r/ω_r'
43	667	—	—
40	667	—	—
32	667	—	—
25	667	—	—
10	710	530	1·34
−15	800	590	1·36
−55	820	610	1·35
−170	850	630	1·35

[a] The values in Table 1 for 25° and above were determined in the present investigation. The remaining figures are those of Giguère[26]. The uncertainty in ω_r is of the order of ± 10 cm^{-1}.

The internal vibrations were treated as independent harmonic oscillators. The internal vibrational frequencies observed in this study (see Experimental section) are listed in Table 2. These values have also been reported by other observers.[26] The bands for the two stretching modes ω_1 and ω_3 are completely merged. In the gas phase, ω_1 and ω_3 are 3825 and 3935 for H_2O and 2758 and 2883 for D_2O.[25] For the internal vibrations, observed values of ω and ω' (Table 2) were used. The internal vibrations contribute the factor Q_v'/Q_v to the total partition function ratio Q'/Q. Thus for the six degrees of freedom for rotation and vibration of liquid H_2O we use three equal librational frequencies (667, 667, 667 cm^{-1}) from Table 1 and three vibrational frequencies (3400, 1645 and 3400 cm^{-1}) from Table 2.

The calculations were based on the equations

$$Q_q \text{ (or } Q_v) = \prod^{3} e^{-u/2}/(1 - e^{-u})$$

$$u = h\nu/kT = hc\omega/kT$$

$$Q'/Q = (M'/M)^{3/2}\, Q_q' Q_v'/Q_q Q_v$$

$$\Delta F = \Delta A = A' - A = -RT \ln Q'/Q$$

$$= -\frac{3}{2} RT \ln (M'/M) - RT \sum^{u'} \ln \frac{e^{-u'/2}}{1 - e^{-u'}} + RT \sum^{u} \ln \frac{e^{-u/2}}{1 - e^{-u}}$$

$$\Delta H = \Delta E = RT^2\, \partial \ln (Q'/Q)/\partial T$$

$$= RT \sum^{u'} \left(\frac{u'}{e^{u'} - 1} + \frac{u'}{2} \right) - RT \sum^{u} \left(\frac{u}{e^{u} - 1} + \frac{u}{2} \right)$$

$$\Delta S = (\Delta H - \Delta F)/T$$

$$\Delta C_p = \partial\, \Delta H/\partial T = R \sum^{u'} \frac{u'^2 e^{u'}}{(e^{u'} - 1)^2} - R \sum^{u} \frac{u^2 e^{u}}{(e^{u} - 1)^2}$$

$$\Delta L = \Delta H_{gas} - \Delta H$$

[26] P. A. Giguère and K. B. Harvey, *Canad. J. Chem.* **34**, 798 (1956).

where Δ before a thermodynamic symbol denotes the quantity for heavy water minus the quantity for light water, h is the Planck constant, k is the Boltzmann constant, T is the absolute temperature (°C + 273·2) and ν or ω is a frequency in sec^{-1} or cm^{-1}.[3,27] The standard states are the liquid waters at 25° and 1 atm pressure, except for ΔH_{gas}, which refers to the gaseous waters under the same conditions. The heat contents are

TABLE 2. INTERNAL FREQUENCIES OF LIQUID WATER AT 25°

Vibrational mode	H_2O, cm^{-1}	D_2O, cm^{-1}
ω_1 stretching	3440	2500
ω_2 bending	1645	1208
ω_3 stretching	3440	2500

referred to the electronic energy minima, *i.e.* zero-point energies are included. The entropies are practical entropies, *i.e.* not including nuclear spin. The calculated ΔH_{gas} of −3549 cal $mole^{-1}$ includes a 103 cal contribution from anharmonicity factors.[3] The uncertainty in the calculated value of ΔH is ±14 cal $mole^{-1}$ associated with a ±10 cm^{-1} uncertainty in ω_r.

Comparison with calorimetrically determined thermodynamic differences for H_2O *and* D_2O

Table 3 offers a comparison of calculated and found thermodynamic differences of

TABLE 3. COMPARISON OF CALCULATED AND CALORIMETRICALLY DETERMINED THERMODYNAMIC DIFFERENCES FOR H_2O AND D_2O AT 25°

ΔG^a	Internal vibrations	Librations[a] ΔG_w	Translations	Calc. value	Found[7–9,33] value
ΔH	−3303·1	−581·9	—	−3885	−3866 ± 23
ΔS	0·034	1·0665	0·3164[b]	1·417	1·439 ± 0·031
ΔF	−3313·2	−900·1	−94·3	−4308	−4295 ± 24
ΔC_p	0·1550	1·166	(0·03)[b]	1·32	1·70
ΔL	—	—	—	336	318

[a] Units of cal $mole^{-1}$ for ΔH, ΔF, and ΔL, and cal deg^{-1} $mole^{-1}$ for ΔS and ΔC_p. ΔG_w will refer to that portion of any thermodynamic difference ΔG_{H_2O} arising from librational (Q_r) differences alone. A Δ before a thermodynamic symbol will designate the quantity for heavy water minus the quantity for light water. [b]The contribution to the entropy from the translations is the same to three figures if they are treated as low frequency oscillations. Their contribution to the heat capacity if treated as such is as shown.

H_2O and D_2O at 25°, and shows the contributions from the different degrees of freedom. The found ΔH is the heat of the reaction

$$D_{2\,gas} + H_2O_{liq} \rightleftharpoons H_{2\,gas} + D_2O_{liq}$$

at 25° (−2096 cal $mole^{-1}$) plus the difference in heat contents $[(H_{298} - H_0)_{D_2} - (H_{298} - H_0)_{H_2} = 24$ cal $mole^{-1}]$[9] and the difference in zero-point vibrational energies (−1794 cal $mole^{-1}$)[9] of D_2 and H_2 at 1 atm and 25°. The agreement with the calculated

[27] For a discussion of partition functions and thermodynamic functions of harmonic oscillators, *cf.* M. Dole, *Introduction to Statistical Thermodynamics* pp. 113f. and 163f. Prentice-Hall, New York (1954). *Cf.* section on *Calculation of isotope effects for ionic hydration* and footnote 34 for practical details of calculations.

values of ΔH, ΔS, ΔF and ΔL (the difference in latent heats of evaporation) is excellent. The value of ΔC_p (the difference in heat capacity) is undoubtedly too small as calculated here and the error is probably due primarily to equating the configurational integrals.

Comparison of the structures of light and heavy water

The water molecule in the liquid phase is prevented from undergoing unrestricted rotational motion due to its coordination with the four surrounding water molecules which make up the solvent "cage". This is the source of the "structure" of liquid water. The stronger the potential interaction between the water molecule within the cell and its neighbors, the greater is the structure, and the higher the value of the librational frequency, which is, therefore, a qualitative measure of the structure. Because of the key importance of the librational frequency it is convenient to define a libration temperature θ as $\theta = hc\omega_r/k = 1{\cdot}439\ \omega_r$ and the difference in libration temperatures between light and heavy water (or solutions in light and heavy water) as $\Delta\theta = hc\ \Delta\omega_r/k = hc(\omega_r - \omega_r')/k$ where $\omega_r' = \omega_r/1{\cdot}3815$.

The structure of heavy water is always greater than that of light water under similar conditions due to its lesser librational thermal energy. Although its potential energy of interaction with other water molecules or solutes is the same as that of light water, the amplitudes of librational oscillations are smaller and thus the kinetic energy is less for heavy water.

Any decrease in structure, e.g. one caused by the addition of solutes, always decreases the librational frequency ω_r and θ and $\Delta\theta$. The quantity θ therefore gives a useful qualitative indication of the structure of H_2O under given conditions. The quantity $\Delta\theta$ always changes in the same direction as the structure difference between light and heavy water (or solutions); therefore, it is a measure of the structure difference. Furthermore, $\Delta\theta$ is a quantitative measure of the structure difference because the thermodynamic differences which arise from the difference in structure can be calculated from it as the only variable. With the introduction of a solute molecule one can determine the new value of the librational frequency to see whether the introduction of the solute molecule has increased or decreased the structure of the water. One may then assign a new structure difference $\Delta\theta$. From values for final and initial states, thermodynamic differences and hence isotope effects may be calculated. The origin of solvent isotope effects observed in light and heavy water is the change in the structure difference $\Delta\theta$ of the two waters from initial to final state.

The librational frequency as a function of the temperature is given in Table 1. In ice the intermolecular forces are very strong and the structure is very ordered. This rigidity is reflected in the high value of the librational frequency and in its slow decrease with increasing temperature. It is obvious that a sharp decrease occurs near the melting point. It has been assumed that the structure difference is independent of temperature in the region of 25° (in accord with the observed constancy of the librational frequency ω_r and $\Delta\theta$ from 25 to at least 43°). Pople's theory of water also points to the fact that while the average value of the angle measuring the extent of bending of the hydrogen bonds increases with rising temperature, the force constant govering this motion is practically constant.[20] There is much independent evidence that the structure difference between the two waters is independent of temperature from approximately 18° to 70°. Wirtz[5], from a consideration of the molecular volumes of the two

liquids and other physical data, concluded that their structure difference was constant over a considerable range of temperature. Baker[28] noted that the viscosity of heavy water equals that of light water at a temperature 8·5° less, from 15° to the highest temperature studied, 35°. A calculation of the heat content differences at temperatures up to 60°, assuming the frequencies to be independent of temperature, closely duplicates the experimentally determined values. One of the most striking features of equilibrium or kinetic isotope effects observed in light and heavy water is the very small or zero value of ΔC_p in the temperature range from approximately 18°–70° as noted by La Mer[15,16] and Robertson[6], although the heat of reaction is not independent of temperature for reactions in either solvent alone, and the isotope effect on the heat of reaction is not constant below 15°. This behavior is explicable only in terms of a structure for water which changes rapidly in the low temperature region and then becomes relatively constant from 18° to 70°.

Ionic hydration equilibria in light and heavy water

The structure of water is controlled by the potential energy of interaction of the water dipoles. The introduction of a charged ion will exert a pronounced effect on this potential energy. Bernal and Fowler[19] concluded that not only water but also all singly charged ions are 4-coordinated in water solution. They defined hydration as occurring only when the potential energy for the ion–water interaction was more negative than that for the water–water interaction. In this sense they concluded that H^+, Li^+, Na^+, all multiply charged ions and OH^- and F^- are hydrated, while the remaining cations and anions are not.

The infrared spectra of ionic solutions. The structure of water is characterized by the frequency of its librational motions. It is natural to determine what effect the addition of ions has on this frequency and hence on the structure of water. Ions exert a pronounced effect upon the librational band of liquid water as can be seen from typical actual spectra in Fig. 2, or more readily from the derived averaged curves in Fig. 3, which were generated by correcting percent absorption for absorption by the empty silver chloride cell and multiplying the resulting percent transmissions by a different scale factor for each solution to obtain equal vertical spreads to facilitate comparison. Due to the broad nature of the librational band, even for pure water itself, one cannot hope to locate new points of maximum absorption with any great certainty or to detect any fine structure. The qualitative conclusions are, however, inescapable. The anions effect the greatest changes. Fluoride ion increases the frequency at which maximum absorption occurs. Chloride, bromide and iodide ions give rise to new regions of maximum absorption at lower frequencies. Lithium ion does not significantly alter the band, but the other singly charged cations absorb at slightly lower frequencies, lower the larger the ion. The internal vibrations undergo no noticeable shifts in frequency. Falk and Giguère[29] have also noted that the addition of simple salts to water solutions brings about a shift in the ω_r band but has little effect on the internal frequencies. The effect of added ions is thus to change the structure difference (and $\Delta\theta$) between light and heavy water. Fluoride ion increases the structure difference, the remaining ions (with the possible exception of lithium ion) decrease it.

[28] W. N. Baker, *J. Chem. Phys.* **4**, 294 (1936).
[29] M. Falk and P. A. Giguère, *Canad. J. Chem.* **35**, 1195 (1957).

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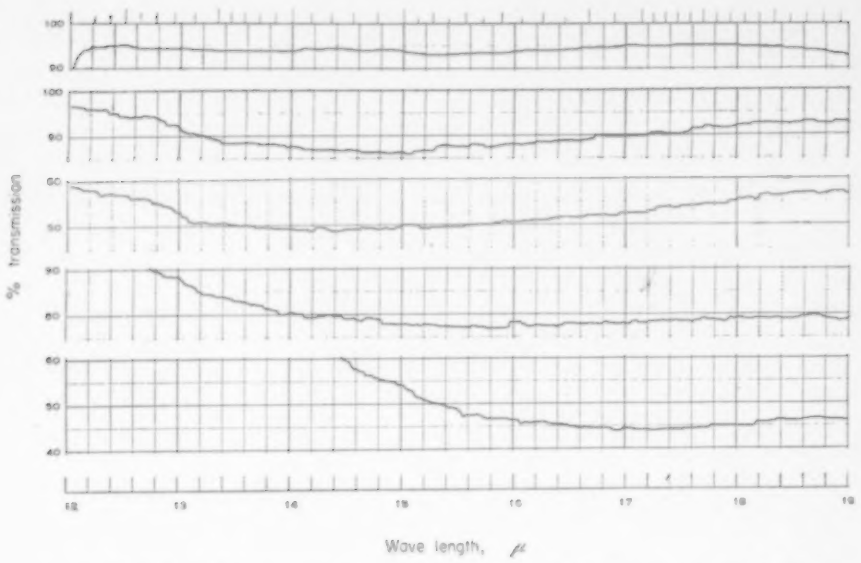

FIG. 2. Typical actual spectra at 25° of (from top to bottom) the empty silver chloride cell, water, sodium fluoride, sodium chloride and lithium bromide solutions.

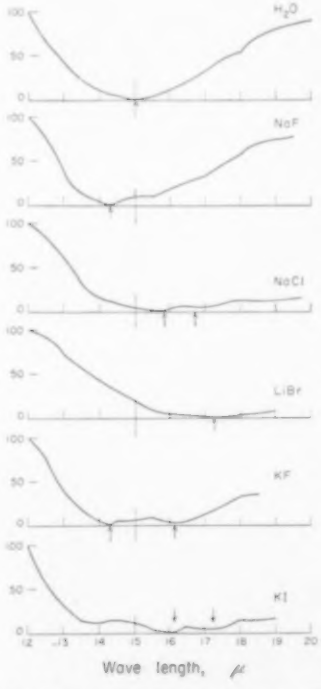

FIG. 3. The librational bands of water and ionic solutions at 25°. Ordinate is percentage of total observed change in percent transmission from maximum to 12 microns.

The librational frequencies observed for water molecules solvating ions should be practically the same at infinite dilution as in the moderately concentrated solutions where they were measured because they are for the relatively tightly held water molecules in the immediate coordination shell. The frequency of the maximum was found to be practically independent of concentration over the range where it was observable. At higher concentrations of salt, the structure of the more remote water molecules also became broken down as evidenced by a wide range of libration frequencies which exhibited no maximum before the cut-off region of the instrument. For example, fluoride ion exhibited the same maximum in solutions of sodium fluoride and potassium fluoride where the ion/water mole ratios were 1/27 and 1/4 respectively. A sodium chloride solution with a chloride/water mole ratio of 1/6 gave a maximum at 596 cm^{-1}, but a more concentrated solution, 1/4·5, gave no maximum, only a continuous increase in absorption down to the cut-off point of the instrument. A lithium chloride solution with a chloride/water mole ratio of 1/9 gave a broad flat maximum from 625–596 cm^{-1}, while a 1/8 solution gave a maximum at 600 cm^{-1} and a 1/4 solution gave a slight maximum at 596 cm^{-1}.

Model for an ion in solution. Consider the replacement of a water molecule in its tetrahedral cell by an ion. Two of the four coordinated water molecules will have to be reoriented in the field of the ion so that each of the four will have one of its hydrogens directed toward the ion if it is an anion or so that each will have its oxygen toward the ion and both hydrogens away if it is a cation. If the ion has a small radius the polarization effect will be large enough to bind the water molecules more tightly than they were previously bound when coordinated about a water molecule. If the ion replacing the central water molecule is large, the water molecules forming the coordination shell are now more loosely bonded than previously in pure water. It is important to note that the orientation and mode of attraction between an ion and a water molecule are different than that of water–water interaction. Thus it does not necessarily follow because a Na^+ ion shows a small decrease in the librational frequency that the water molecules forming the coordination shell are more loosely held than in the absence of the ion. However, a large decrease in the librational frequency such as that noted for the Cl^- ion undoubtedly does imply looser binding.

Calculation of isotope effects for ionic hydration. The present goal is to calculate the differences in thermodynamic quantities associated with the introduction of a gaseous ion into light and heavy water at infinite dilution. This is to be attempted in the following fashion. Within the radius of the coordination shell of four water molecules, water does not behave as a dielectric medium.[19,30] The heat and entropy differences for the coordinated water molecules will be calculated by the statistical mechanical method from the pure water and solution librational frequencies. Beyond the coordination sphere the field due to the ion is less than the saturation value for water, normal dielectric properties are again assumed for the solvent, and the thermodynamic changes are derived from "Born charging" effects.

Dielectric constants were determined for light and heavy water over a range of temperatures by Wyman and Ingalls[31], who noted that they were much too similar to explain differences in ionic heats of solution. Employing a radius equal to that of the ion[32]

[30] D. D. Eley and M. G. Evans, *Trans. Faraday Soc.* **34**, 1093 (1938).
[31] J. Wyman, Jr. and E. N. Ingalls, *J. Amer. Chem. Soc.* **60**, 1182 (1938).
[32] All ionic radii employed in this paper are those given by V. M. Goldschmidt, *Trans. Faraday Soc.* **25**, 253 (1929).

plus the diameter of the water molecule (2·76 Å) in the formulas for Born charging effects gives heat differences between D_2O and H_2O of only 7 cal mole^{-1} and free energies of only 2 cal mole^{-1} for the ions considered in this paper. A difference of 7 cal mole^{-1} is equivalent to an error of 1 cm^{-1} in the librational frequencies. It does not seem realistic to retain a value which is small relative to the differences arising from the innermost shell and is actually less than the uncertainties of both the experimental and calculated values.

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Therefore essentially all of the isotope effect on a heat or entropy of ionic solution at infinite dilution must have its origin in the motions of the four coordinated water molecules. The internal vibrations of the water molecules are taken as unchanged in the resulting solution,[33] and since there are practically identical potential fields for isotopic molecules there will be no direct contribution to the isotope effect from the monatomic ion itself. All of the thermodynamic differences for ionic solution in light and heavy water will arise from differences in the librational frequencies alone, i.e. from changes in $\Delta\theta$. Therefore, the difference in free energy of the four coordinated light and heavy water molecules upon changing coordination from a central water molecule to an ion is

$$\Delta F_s = 4RT \ln \left(\frac{Q_q}{Q_q'}\right)_i \left(\frac{Q_q'}{Q_q}\right)_w \tag{1}$$

where the partition function ratio $(Q_q/Q_q')_i$ is determined by the $\Delta\theta$ between the two ionic solutions, $(Q_q'/Q_q)_w$ is determined by the $\Delta\theta$ between the two pure waters, and the factor of four arises from the assumption that four water molecules are coordinated.

Thus the librational frequency is to be employed to determine all of the thermodynamic differences. The calculations will of course be carried out for individual ions. Since the maximum for the librational band in an observed spectrum is difficult to pin down exactly due to the broad nature of the band and overlapping effects, it will be more practical to begin with the observed frequency for one ion with a clear maximum in its spectrum. From this value and observed[10] differences in heats of solution of salts in light and heavy water (Table 4), the individual heats of all of the other ions may be tabulated (Table 5). The corresponding values for the librational frequencies may then be determined for these remaining ions by performing the calculation in reverse, and the values for the librational frequencies thus obtained compared with the experimental observations (Table 6). By proceeding in this manner the theory may be compared with experiment and at the same time the best values for the corresponding entropies obtained. The fluoride ion exhibits a maximum in the librational band at 698 cm^{-1} in solutions of both sodium fluoride and potassium fluoride (see Fig. 3). The librational frequency for this ion and that for pure water (667 cm^{-1}) are taken as the basis for the calculations. The quantities ΔH_w, ΔS_w and ΔF_w (Table 3 footnote *a*) are calculated for three-dimensional isotropic harmonic oscillators of frequencies ω_r and $\omega_r' = \omega_r/1{\cdot}3815$. The quantities ΔH_i, ΔS_i and ΔF_i are determined in a similar fashion from $\Delta\theta_i$, the new value of $\Delta\theta$ for the ionic solution in H_2O. For example, the isotope effect on the heat of solution of a gaseous ion in light and heavy water is $\Delta H_s = 4\,\Delta H_i - 4\,\Delta H_w$ where $4\,\Delta H_i$ is the difference in *librational* heat contents of four heavy and four light water molecules coordinated to an ion in solution

[33] A small change in value of an internal frequency will not sensibly affect the zero-point energy difference, and the Einstein contributions from these frequencies are negligible. Furthermore, a structure-breaking ion would tend to raise ω_1 and ω_2 but lower the bending mode ω_2. The reverse would be true for a structure-forming ion. Thus for any one ion the small changes in frequency would tend to compensate.

and 4 ΔH_w is the difference in librational heat contents of four heavy and four light water molecules coordinated to a water molecule in pure liquid water. The quantity ΔH_s is the difference in the heats of the two reactions

$$X^{\ominus}_{gas} + 4D_2O_{liq} \rightleftharpoons X^{\ominus}(4D_2O)_s \tag{2}$$

$$X^{\ominus}_{gas} + 4H_2O_{liq} \rightleftharpoons X^{\ominus}(4H_2O)_s \tag{3}$$

and is therefore the heat of the reaction

$$X^{\ominus}(4H_2O)_s + 4D_2O \rightleftharpoons X^{\ominus}(4D_2O)_s + 4H_2O \tag{4}$$

for transfer of an ion from light to heavy water.[34]

TABLE 4. ISOTOPE EFFECTS[10] FOR HEAT OF SOLUTION AT 25°

Salt	ΔH_s cal mole^{-1}
LiCl	400
NaCl	560
KF	60
KCl	615
KBr	750
KI	890
RbBr	790
CsBr	815

TABLE 5. CALCULATED ISOTOPIC DIFFERENCES FOR INDIVIDUAL IONIC HEATS, ENTROPIES AND FREE ENERGIES OF SOLUTION IN LIGHT AND HEAVY WATER AT 25°[a]

Ion	Radius Å	ω_r cm^{-1}	$-4\ \Delta H_i$	$4\ \Delta S_i$	ΔH_s	ΔS_s	ΔF_s	$\log \frac{\gamma_{D_2O}}{\gamma_{H_2O}}$
F^-	1·35	(698)[b]	2503	4·048	−175	−0·218	−110	−0·0806
Cl^-	1·81	598	1948	4·758	+380	+0·492	+233	+0·171
Br^-	1·96	573	1813	4·949	515	0·683	311	0·228
I^-	2·20	546	1673	5·138	655	0·872	395	0·290
		587[c]	2830[c]	7·240[c]	662[c]	0·841[c]	411[c]	0·308[c]
Li^+	0·78	664	2308	4·285	20	0·019	14	0·00103
Na^+	0·98	635	2148	4·491	180	0·225	113	0·0828
K^+	1·33	625	2093	4·571	235	0·305	144	0·106
Rb^+	1·49	618	2053	4·615	275	0·349	171	0·125
Cs^+	1·65	613	2028	4·652	300	0·386	185	0·136

[a] Units of cal mole-ion^{-1} for all ΔH and ΔF, and cal deg^{-1} mole-ion^{-1} for all ΔS. Data for water: $\omega_r' = 667$ cm^{-1}; $4\ \Delta H_w = -2328$ cal mole^{-1}; $4\ \Delta S_w = 4{\cdot}266$ cal deg^{-1} mole^{-1}; $4\ \Delta F_w = -3600$ cal mole^{-1}. [b] This frequency is the observed one. All others are calculated as explained in the text. [c] The second set of values for I^- is calculated assuming a coordination number of 6.

[34] The isotope effects are easily calculated using the tabulated values of the Einstein functions given in Dole[27]. For each value of θ/T the values of

$$\frac{H^\circ}{RT} = \left(\frac{\theta/T}{e^{\theta/T}-1}\right);\quad \frac{S^\circ}{R} = \left(\frac{\theta/T}{e^{\theta/T}-1}\right) - \ln(1-e^{-\theta/T});\quad \frac{F^\circ}{RT} = -\ln Q^\circ = \ln(1-e^{-\theta/T})$$

are tabulated. The quantities H°, F°, and Q° as calculated from Dole's tables do not include the zero-point energy contribution, which for three degrees of freedom is $3R\theta/2$, or $-3R\ \Delta\theta/2$ for the difference between heavy and light water. For example, the isotope effect on the heat of solution is

$$\Delta H_s = 4\ \Delta H_s - 4\ \Delta H_w = 4\left(-\frac{3}{2}R\ \Delta\theta_s + 3\ \Delta H_s^\circ\right) - 4\left(-\frac{3}{2}R\ \Delta\theta_w + 3\ \Delta H_w^\circ\right)$$

A graph was constructed giving $4^\circ\Delta H_s$ vs. ω_r for convenience in deriving Table 5.

Isotopic differences in heats of solution, listed in Table 4, were shown[10] to be independent of concentration below 0·5 moles of salt per 100 moles of water and so are valid for infinite dilution. The results of the calculations are given in Table 5. Although the band maxima cannot be located accurately, we have listed in Table 6 the observed regions ($\pm 10\ cm^{-1}$) of maximum absorption (*cf.* Fig. 3). In every case the band extends to the frequencies calculated for the different ions. Spectra of lithium chloride solutions show that the lithium ion leaves the water band undisturbed. No new

TABLE 6. COMPARISON OF CALCULATED AND OBSERVED LIBRATIONAL FREQUENCIES

Ion	Calc. ω_r, cm^{-1}, for		Obs cm^{-1}
	4-coord	6-coord	
F^-	(698)	—	698
Cl^-	598	621	600
Br^-	573	604	580
I^-	546	587	580
Li^+	664	—	(667)
Na^+	635	—	630
K^+	625	—	620
(H_2O)	—	—	(667)

maximum was observable for this ion in lithium chloride or lithium bromide solutions. Therefore, the value for pure water has been entered in parentheses for this ion in Table 6. The agreement between the second and fourth columns in Table 6 (with the exception of the iodide ion which is discussed below) is very satisfactory. The agreement provides some *a posteriori* justification for the approximations which have been made and suggests that the isotope effect for the heat of solution of an ionic solute in light and heavy water is indeed due to changes in the structure difference between the two waters. The agreement in Table 6 is very dependent upon the number of water molecules which are assumed to be coordinated to the ion. The calculated values of the librational frequencies were arrived at by assuming a coordination number of four. Table 6 also shows the results of calculations of the librational frequency for the largest ions (Cl^-, Br^- and I^-) if coordination numbers of six are assumed. This change in coordination number produces a change in the calculated librational frequency large enough to be detected experimentally. The results suggest that while the chloride and bromide ions are four-coordinated in aqueous solution, the iodide ion may well be six-coordinated, a reasonable result since it is the largest of these anions.

Multiply-charged ions. Although no measurements were made with multiply-charged ions in this study, one can calculate in the same way from heats of solution[10] that the water molecules coordinated to Mg^{++} and the heavier alkaline earth ions would also have very slightly decreased librational frequencies, structures and structure differences $\Delta\theta$. These calculations were made assuming a coordination number of 6. If the coordination number were 4 the shifts would still be in the same direction, but slightly larger.

Heats of solution. Addition of the values ΔH_s for any anion-cation pair gives the isotopic difference for heat of solution of the salt in light and heavy water. Only the

fluoride ion increases the librational frequency of the water molecules and hence the structure difference. Therefore, it is the only singly charged ion for which more heat is evolved in heavy than in light water. All of the other singly-charged ions decrease the librational frequency of water and hence more heat is evolved from their solution in light than in heavy water. Fig. 4 shows a plot of ΔH_s *vs.* the ionic radius. There is a sharp break between Na^+ and K^+ in the ΔH_s curve. This agrees with the calculations of Bernal and Fowler[19] that Li^+ and Na^+ are more strongly bonded to their coordinated water molecules than water itself whereas K^+, Rb^+ and Cs^+ are not. Once the

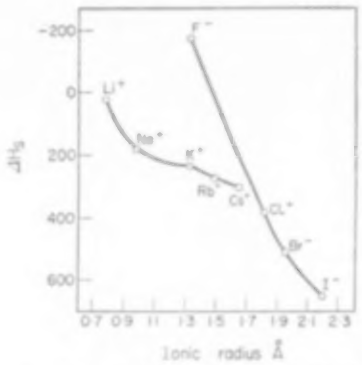

FIG. 4. The isotope effect for the ionic heat of solution in light and heavy water ΔH_s in cal mole-ion^{-1} vs. the ionic radius, at 25°.

bonding becomes weaker, any further structure breaking is due more to the mere increase in size of the ions and less to the polarization changes, which become relatively small as the ionic radius is increased. This same change in slope with increasing ionic radius is exhibited in a curve of mutual potential energy for water molecules and singly-charged ions.[19] This parallelism is to be expected because the isotope effects refer to differences in kinetic energy of the coordinated water molecules, and these kinetic motions are determined by the potential energy.

Entropies of solution. The changes in ΔS_s parallel those for ΔH_s. Only the fluoride ion increases the librational frequency and thus leads to a greater loss of entropy for its solution in heavy water as opposed to its solution in light water. The remaining singly-charged ions, with the possible exception of the lithium ion, break down the structure of the water (decrease $\Delta\theta$) and lead to a smaller loss in entropy in heavy water. Frank[35] has pointed out that an ionic solution appears to have too much entropy. Solution of two argon gas molecules in water leads to a greater entropy loss than when potassium chloride is dissolved in water. Potassium and chloride ions have the same electronic structure as an argon atom. The effect of the charge is thus to *lessen* the entropy decrease. The explanation of this seemingly contrary result given by Frank is now generally accepted. A large part of the entropy decrease arises from the restriction of the ion in its "box" in solution as opposed to its complete freedom in the gas phase. This is a free volume effect. There is a smaller contribution from the Born charging effect which Frank also considers as arising only outside of the primary coordination shell. Frank employed the geometric model of Bernal and Fowler and

[35] H. S. Frank and M. W. Evans, *J. Chem. Phys.* **13**, 507 (1945).

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considered each ion as coordinated with four water molecules. However, this is as far as he accepted the model, for he always considered water as coordinated more tightly to the ion than to water in pure water no matter what the ionic radius. For the entropy change of the water molecules coordinated to the ion, he used 4 times one half of the entropy decrease of a water molecule changing from liquid to ice. Thus he always considered the water as more tightly bound and more restricted in its movement when bound to the ion than when bound to water. Adding these contributions he finds that he has too little entropy, i.e. his result is too negative. To bring the quantities back into line he postulates a "fluctuation entropy" which arises in the outer layers of the water molecules surrounding the primary coordination shell. The presence of the ion and the reorientation of the water molecules about the ion disrupts the structure of the surrounding water molecules in the immediate vicinity. In this boundary layer the structure of water will be broken down because the ion with its coordination sphere no longer fits in with the general structural pattern of water. Inserting values for the known results and all of the other factors but the fluctuation entropy, he has solved for and tabulated the latter quantity.

From the spectra of ionic solutions and from the isotope effects it would seem that, aside from the fluoride ion, all of the singly-charged ions decrease the librational frequency of the water molecules coordinated to the ion. These water molecules must have more kinetic freedom since the energy levels for water molecules bound to ions other than fluoride are closer together than for pure water; otherwise the heat and entropy effects for the solution of ions in water would show an isotope effect in the other direction, as they do for the fluoride ion. Thus the assumption of Frank that the water molecules in the coordination sphere undergo one half of the entropy of freezing to ice is seemingly invalid. When one removes this negative contribution of approximately 12 cal deg^{-1} mole-ion^{-1} and replaces it with a positive one which represents the fact that for all of the ions but fluoride the water molecules in the coordination shell actually possess more kinetic freedom than previously, then the discrepancy that ions seem to have too much entropy disappears and with it the need to postulate a fluctuation entropy. The values tabulated by Frank for the fluctuation entropy parallel the isotope effects and spectral results perfectly. Thus, fluoride ion is the only anion with a negative fluctuation entropy, lithium ion has one close to zero and other ions have positive fluctuation entropies increasing with ionic radius.[36]

Probably, at least for the larger ions, a structure breaking effect does occur beyond the primary coordination shell but the effect is much smaller than supposed (by at least 12 cal deg^{-1} deg^{-1} mole-ion^{-1}).

Free energies of solution. The free energies illustrate that solution in light water is favored over solution in heavy water for all the singly charged ions except fluoride ion. The ΔF_s values are the free energy differences between reactions 2 and 3 at infinite dilution

$$\Delta F_s = F_s^{D_2O} - F_s^{H_2O} = -RT \ln K_{D_2O}/K_{H_2O} = RT \ln \gamma_{D_2O}/\gamma_{H_2O}$$

where the standard state for the ion is an ideal gas at 1 atm pressure, and $F_s^{D_2O}$ and $F_s^{H_2O}$, K_{D_2O} and K_{H_2O}, and γ_{D_2O} and γ_{H_2O} are the corresponding free energies of solution, equilibrium constants and individual ionic activity coefficients for equations

[36] Frank and Evans have tabulated values for the process of vaporization of the ion from solution. Since we are considering the reverse of this process the algebraic sign of the fluctuation entropies is reversed.

2 and 3 respectively. Therefore ΔF_s is the free energy of transfer of an anion from light to heavy water at infinite dilution (the free energy of equation 4).

Although this activity coefficient ratio is defined for infinite dilution, it is probable that it generally changes very little at higher concentrations. For example, the difference in voltages of the cells

$$\text{Cd–Hg (2 phase)/CdI}_2\ (m \text{ in } H_2O)\text{/AgI–Ag}$$

$$\text{Cd–Hg (2 phase)/CdI}_2\ (m \text{ in } 90\%\ D_2O)\text{/AgI–Ag}$$

changes by only 0·00451 volts over the range from 0·00573m (moles of salt per 55·51 moles of solvent) to 1·359m, showing that even with ions as large as Cd^{++} and I^-, $\Delta F_s^{Cd^{++}} + 2\,\Delta F_s^{I^-}$ does not change by more than −208 cal per mole of salt and $\log(\gamma_{D_2O}/\gamma_{H_2O})$ does not change by more than 0·153.[17]

The ΔF_s values should parallel the solubility ratios of the ions in the two waters. A number of solubilities were determined in light and heavy water by Menzies[4,11]. The solubility ratios m_{H_2O}/m_{D_2O}, expressed in moles of solute per 55·51 moles of solvent are all greater than unity for the salts studied and increase as the ionic radii of the ions comprising the salt increase: e.g. m_{H_2O}/m_{D_2O} is 1·07 for NaCl, 1·10 for KCl and 1·12 for KBr. This order is in accord with the calculated values of ΔF_s.

The ratios of the molalities will not give the ΔF_s values precisely because at saturation the unequal solubility of a salt in the two waters will require an activity coefficient correction

$$\Delta F_s = RT \ln \left(\frac{\gamma^+_{D_2O}\gamma^-_{D_2O}}{\gamma^+_{H_2O}\gamma^-_{H_2O}} \right) = RT \ln \left(\frac{m_{H_2O}\beta_{H_2O}}{m_{D_2O}\beta_{D_2O}} \right)^2 \tag{5}$$

where the mean ionic activity coefficients β calculated from the Debye–Hückel theory reduce to unity at infinite dilution. The dielectric properties of the two waters are so nearly identical that β_{D_2O} equals β_{H_2O} when the molalities of the salt are the same in the two solvents at low concentrations. Due to the high solubility of the salts referred to above, no satisfactory estimate of $\beta_{H_2O}/\beta_{D_2O}$ may be made. However, it is possible to make this correction in the case of the much less soluble salt lithium fluoride, which according to the calculations should be the only uni-univalent salt to be more soluble in heavy water than in light water. The relative solubility of lithium fluoride has been determined in the two waters[37] and it is indeed more soluble in the heavy solvent. Using

$$-\log \beta = \frac{0{\cdot}509\sqrt{\mu}}{1 + 1{\cdot}45\sqrt{\mu}}$$

where μ is the ionic strength to calculate the β values, the solubility ratio m_{D_2O}/m_{H_2O} is calculated to be 1·11. The experimental value is 1·15.

Kinetic solvent isotope effects

The direction and magnitude of kinetic solvent isotope effects (not due to transfer of a proton in the rate-controlling step) are determined by the difference in $\Delta\theta$ between the transition state and the reactants. A reaction which destroys the structure of the water in the formation of the transition state (by the creation of charge) will proceed

[37] H. W. Birnthaler and E. Lange, *Z. Electrochem.* **43**, 649 (1937).

more rapidly in light water. A reaction which returns structure to the solvent when the transition state is reached (by neutralization or distribution of charge) will exhibit an enhanced rate in heavy water. These concepts will be expanded and exemplified in later papers.[38]

Hydronium and hydroxide ions

Hydronium and hydroxide ions contain exchangeable hydrogen atoms and therefore the degrees of freedom of the ions themselves will contribute to their thermodynamic differences when they are solvated by the two waters.

Noonan and La Mer[14] studied the two cells

$$D_2 \,|DCl\ (m \text{ in } D_2O)|\ AgCl\text{–}Ag$$

$$H_2 \,|HCl\ (m \text{ in } H_2O)|\ AgCl\text{–}Ag$$

over a range of temperatures. They were thus able to determine the free energy, heat content and entropy changes for the reaction

$$\tfrac{1}{2}D_2 + HCl(H_2O) \rightleftarrows \tfrac{1}{2}H_2 + DCl(D_2O) \qquad (6)$$

As they noted, equation 6 and its measured thermodynamic properties do not allow one to determine any of the differences between the two hydronium ions since the reaction involves the transfer of the chloride ion from light to heavy water. Experimental thermodynamics yields information pertaining to a pair of ions only. However, the present theory permits one to determine individual ionic differences for the transfer of an ion between the two waters and thus equation 6 may be employed in conjunction with the theory for the determination of the thermodynamic differences between D_3O^+ and H_3O^+. By proceeding in this fashion the values obtained will be based on the same scale as all of the others ions as originally fixed by the frequency value assigned to fluoride ion and the heat data for the monatomic ions. Equation 6 may be written as

$$\tfrac{1}{2}D_{2\ gas} + H_3O^{\oplus}(4H_2O)_s + Cl^{\ominus}(4H_2O)_s + D_2O_{liq} + 2(4D_2O)_{liq} \rightleftarrows$$

$$\tfrac{1}{2}H_{2\ gas} + D_3O^{\oplus}(4D_2O)_s + Cl^{\ominus}(4D_2O)_s + H_2O_{liq} + 2(4H_2O)_{liq}$$

Employing values determined above for the thermodynamic differences for chloride ion (ΔG_i) and for the pure waters (ΔG_w), and measured[9] differences for the pure waters (ΔG_{H_2O}) and the two forms of hydrogen gas, one obtains $\Delta H_i = -7579$ cal mole-ion^{-1}, $\Delta S_i = 6{\cdot}173$ cal deg^{-1} mole-ion^{-1} and $\Delta F_i = -9419$ cal mole-ion^{-1} for H_3O^+ at 25°.

Furthermore, it is possible through the use of infrared and Raman techniques to obtain sufficient spectroscopic data on the hydronium and deuteronium ions in light and heavy water solutions respectively to calculate ΔH_i, ΔS_i and ΔF_i from first principles. The values determined in this manner are completely independent of those determined above. The values of the internal vibrations employed in the calculations were those obtained by Ferriso and Hornig[39] from their investigation of the infrared spectra of $H_3O^+\,Cl^-$ and $D_3O^+Cl^-$. We have observed essentially the same spectra for solutions of HCl and DCl in light and heavy water respectively, as have Falk and

[38] E.g. C. G. Swain, A. D. Ketley and R. F. W. Bader, *J. Amer. Chem. Soc.* **81**, 2353 (1959).
[39] C. C. Ferriso and D. F. Hornig, *J. Chem. Phys.* **23**, 1464 (1955).

Giguère[29]. The only change from the solid state was a broadening of the bands. Investigations of acidic solutions in the potassium bromide region of the infrared indicated that the hydronium ion leaves the structure of water undisturbed since it leaves the libration band of water unchanged. The rotational motions of the hydronium ion as well as those of the coordinated water molecules will be restricted in solution. Ferriso and Hornig noted a band at 770 cm^{-1} in solid $H_3O^+Cl^-$ which they ascribed to a librational motion of the ion. We found a Raman band for the ion in solution at 643 cm^{-1} for HCl and 465 cm^{-1} for DCl. These may be treated like the hindered rotations of the water molecules. From these data one calculates the following thermodynamic differences: $\Delta H_i = -7456$ cal mole-ion^{-1}, $\Delta S_i = 6{\cdot}082$ cal deg^{-1} mole-ion^{-1} and $\Delta F_i = -9270$ cal mole-ion^{-1}. These values differ from the corresponding ones determined with the aid of the theory by only small amounts. This agreement is evidence for the reasonableness of the values so determined and a check on the assignment of the individual ionic heat and entropy differences.

It is now possible to calculate the equilibrium constant for the exchange process

$$2D_3O^{\oplus}(4D_2O) + 2(4H_2O) + 3H_2O \rightleftharpoons 2H_3O^{\oplus}(4H_2O) + 2(4D_2O) + 3D_2O \quad (7)$$

using the experimental value for ΔF_{H_2O}.[9] The free energy change for this reaction is calculated to be -1247 cal and hence the equilibrium constant is 8·200 at 25°.[2] This value indicates that the deuteronium ion in heavy water is a stronger acid than the hydronium ion in light water. The significance of this result in relation to both equilibrium and kinetic studies is fully discussed in part II.[2]

Wynne-Jones[40] determined the ionization constant for heavy water at a number of temperatures. His value for this constant at 25° agrees with that obtained by Abel *et al.*[41] The ratio of the ionization constants for light and heavy water K_{H_2O}/K_{D_2O} determines the equilibrium constant for the exchange reaction

$$2(4D_2O) + 2D_2O + H_3O^{\oplus}(4H_2O) + HO^{\ominus}(4H_2O) \rightleftharpoons 2(4H_2O) + 2H_2O + D_3O^{\oplus}(4D_2O) + DO^{\ominus}(4D_2O) \quad (8)$$

The values of ΔH and ΔS for this change in state as determined by Wynne-Jones at 25° are 970 ± 50 cal and 0·0054 cal deg^{-1} respectively. Since the thermodynamic differences between D_3O^+ and H_3O^+ have been calculated from the theory previously, equation 8 may be used to determine the thermodynamic differences between DO^- and HO^-. These values for the hydroxide ion are $\Delta H_i = -3839$ cal mole-ion^{-1}, $\Delta S_i = 5{\cdot}242$ cal deg^{-1} mole-ion^{-1} and $\Delta F_i = -5402$ cal mole-ion^{-1}.

Aqueous solutions of sodium hydroxide were examined in the potassium bromide region of the infrared. The results indicated that the hydroxide ion leaves the librational band of liquid water undisturbed. Thus the hydroxide ion, like the hydronium ion, does not exert a solvent isotope effect by changing the structure of liquid water, and differences between DO^- and HO^- are due principally to differences in vibrations and rotation of the ions themselves. An *a priori* calculation of the thermodynamic differences for deuteroxide and hydroxide ions similar to that performed for the deuteronium and hydronium ions suggests that the hydroxide ion also experiences a barrier to free rotation in aqueous solution. The hindering potential in this case is

[40] W. F. K. Wynne-Jones, *Trans. Faraday Soc.* **32**, 1397 (1936).
[41] E. Abel, E. Bratu and O. Redlich, *Z. Physik. Chem.* **A173**, 353 (1935).

much smaller than those encountered for water or the hydronium ion since the librational frequency in this case is judged to be in the region of 475 cm^{-1}.

The relative basicity of the two ions is determined by the equilibrium

$$2DO^{\ominus}(4D_2O) + 2(4H_2O) + H_2O \rightleftharpoons 2HO^{\ominus}(4H_2O) + 2(4D_2O) + D_2O \qquad (9)$$

for which ΔF is calculated to be -691 cal. The value of the equilibrium constant is therefore 3·21. Deuteroxide ion in heavy water is thus a stronger base than hydroxide ion in light water. This result is in agreement with observations obtained from kinetic studies. Basic hydrolyses and reactions which are base-catalyzed proceed more rapidly in heavy water than in light water.

EXPERIMENTAL

The infrared spectra of liquid light and heavy water and ionic solutions were obtained by pressing thin films of the liquids between two silver chloride plates, each 1 mm thick. A Baird Model AB-2 double-beam recording spectrophotometer fitted with a sodium chloride prism was used to observe the three internal frequencies of the water molecules. The values thus obtained are listed in Table 1. The librational frequency of liquid water was observed with a potassium bromide prism (which transmits down to 360 cm^{-1}). Frequencies for maximum absorption ranging from 725 cm^{-1} to 550 cm^{-1} were observed depending upon the temperature and the nature of added solute molecules.

The temperature was controlled by circulating a stream of water from a constant temperature bath through metal tubing attached directly to the metal micro-cell holder. The silver chloride plates were clamped in a metal frame which in turn was held flush against the metal holder within the instrument. The temperature of the cell was determined by placing an iron-constantan thermocouple lead in a small hole drilled through one of the silver chloride plates. The thermocouple lead was thus in intimate contact with the cell window and with the film of liquid. Since the film was very thin, the transfer of heat between it and the cell windows was almost instantaneous. Sufficient time was allowed for the complete system to attain temperature equilibrium. Thermocouple voltages were measured with a Leeds and Northrup K-2 potentiometer. The results obtained are listed in Tables 1, 2 and 6. Further details on the spectroscopic equipment and procedure used have been published in the third paper of this series.[35]

Acknowledgement—We are indebted to Prof. Walter H. Stockmayer for helpful suggestions and discussions.

Tetrahedron, 1960, Vol. 10, pp. 200 to 211. Pergamon Press Ltd. Printed in Northern Ireland

A THEORETICAL INTERPRETATION OF ISOTOPE EFFECTS IN MIXTURES OF LIGHT AND HEAVY WATER[1-3]—II

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(*Received* 19 *October* 1959; *in revised form* 28 *March* 1960)

Abstract—Solvent isotope effects for H_2O—D_2O mixtures and for ionic hydration equilibria in such mixtures can be calculated from the structure difference between D_2O and H_2O and that between HDO and H_2O and the relative amounts of the three waters. The behavior of acids in H_2O—D_2O mixtures is considered in detail. Dissociation constants of acetic acid are calculated over the complete range of deuterium concentrations and found to agree with the experimentally determined ones. The Gross equation for the dependence of isotope effect on mole fraction of deuterium for acid-catalyzed reactions of substrates S proceeding via SL^+ transition states (L = H or D) is derived from first principles.

THE previous paper[2] was concerned with differences between pure light and pure heavy water or between ionic solutions in these solvents. The present paper will be concerned with differences between light water and mixtures of light and heavy water.

The first step in the discussion of isotope effects observed in mixtures of light and heavy water is the calculation of differences in thermodynamic properties between these mixtures and pure light water. For one mole of a mixture of H_2O, D_2O and HDO, the value of any extensive thermodynamic function G is given by

$$G = \Sigma N_j \bar{G}_j$$

where $\bar{G}_j$ are partial molal quantities and N_j are solvent mole fractions

$$\Sigma N_j = 1 \qquad (1)$$

Since mixtures of the three isotopic forms of water, H_2O, D_2O and HDO, are ideal solutions,

$$\bar{G}_j = G_j + G_j^m$$

where G_j is the value of the property G for one mole of the pure component j and G_j^m is the change in G_j from mixing in one mole of this component to form the ideal solution (e.g. $F_j^m = RT \ln N_j$). Now

$$G - G_1 = \Sigma_j N_j \bar{G}_j - G_1 = \Sigma_j N_j (G_j - G_1) + \Sigma_j N_j G_j^m$$

where the subscript 1 refers to H_2O, 2 to D_2O and 3 to HDO. The part of $G - G_1$ due to the properties of the component waters is defined as the isotopic excess function ΔG

$$\Delta G = \Sigma_j N_j (G_j - G_1) \qquad (2)$$

[1] Supported in part by the Atomic Energy Commission under Contract No AT(30-1)-905 and by the National Institutes of Health under Research Grant RG-3711 (C4 and C6).
[2] *Cf.* Part I: C. G. Swain and R. F. W. Bader, *Tetrahedron* **10**, 182 (1960).
[3] For further details, *cf.* R. F. W. Bader, Ph.D. Thesis in Organic Chemistry, M.I.T., December, 1957.

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The thermodynamic differences characterizing any structure difference between a mixture and pure H_2O, or between solutions of ions in these solvents, are evaluated by considering only those contributions to the terms $(G_j - G_1)$ in equation 2 which arise from the librational degrees of freedom. The term $(H_2 - H_1)$ determined by only the librational motions was previously[2] designated as $\Delta H(= H^{D_2O} - H^{H_2O} = H_w' - H_w)$ and calculated to be -582 cal mole^{-1}, by treating the librational degrees of freedom as arising from isotropic three-dimensional harmonic oscillators of frequency ω_r and $\omega_r(I/I')^{1/2}$ where ω_r is the observed librational frequency of the light water molecule and I/I' is the mean of the ratios of the three principal moments of inertia for H_2O and D_2O molecules. The present ΔG_w quantities will also contain a librational contribution from the term $G_3 - G_1(= G_w^{HDO} - G_w^{H_2O} = G_w'' - G_w)$ and this may be calculated from the value of ω_r in a similar fashion by assuming the librational frequency of an HDO molecule to be given by

$$\omega_r'' = \omega_r(I/I'')^{1/2}$$

where I/I'' is the mean of the ratios of moments of inertia for H_2O and HDO molecules. The factor $(I/I'')^{1/2}$ has a value of 1/1·1884. Therefore structure differences will be governed by the three librational frequencies ω_r (667 cm^{-1}), ω_r' (482 cm^{-1}) and ω_r'' (561 cm^{-1}). An almost identical result would have been obtained for ω_r'' (566 cm^{-1}) by employing the rule of the geometric mean.[4] The isotopic excess functions which characterize the structure differences between H_2O—D_2O mixtures and pure H_2O can now be calculated to be

$$\Delta H_w = -581{\cdot}9N_{D_2O} - 348{\cdot}0N_{HDO}$$

$$\Delta S_w = 1{\cdot}067N_{D_2O} + 0{\cdot}521N_{HDO}$$

$$\Delta F_w = -900{\cdot}1N_{D_2O} - 503{\cdot}4N_{HDO}$$

The equilibrium constant K_1 for the reaction

$$H_2O + D_2O \rightleftarrows 2HDO \tag{3}$$

has a value of 3·96 at 25°,[5] and the mole fraction of deuterium α is given by

$$\alpha = (2N_{D_2O} + N_{HDO})/2 \tag{4}$$

The values of the isotopic excess functions which characterize the structure differences between H_2O—D_2O mixtures and pure H_2O are shown in Fig. 1 as a function of the mole fraction of deuterium, α. The values of ΔH_w, $T\Delta S_w$ and ΔF_w are almost linear functions of α.

The solvent isotope effects, i.e. those due only to a change in the structure difference and not involving isotopic exchange with the substrate, should exhibit this same almost linear behavior. The addition of an anion to a solution of the light and heavy waters will change the librational frequencies of the water molecules in the 4-coordinated shell of the ion and thus the structure differences from those of the pure waters at that particular value of α. Calculations are done as before (Ref. 2, footnote 34) except that from the one new librational frequency for H_2O both ω_r' and ω_r'' and

[4] G. N. Lewis and R. E. Cornish, *J. Amer. Chem. Soc.* **55**, 2616 (1933); B. Topley and H. Eyring, *J. Chem. Phys.* **2**, 217 (1934); J. Bigeleisen, *Ibid.* **23**, 2264 (1955).

[5] H. C. Urey, *J. Chem. Soc.* 569 (1947).

hence both $\Delta\theta$ values are calculated. The resulting thermodynamic differences $G_{D_2O} - G_{H_2O}$ and $G_{HDO} - G_{H_2O}$ calculated from the two $\Delta\theta$ values are multiplied

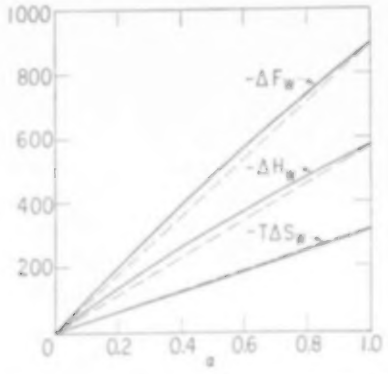

FIG. 1. The value of the isotopic excess functions characterizing the structure difference between H_2O—D_2O mixtures and light water at 25° in cal mole^{-1} as a function of the mole fraction of deuterium (D/D + H).

by the mole fractions N_{D_2O} and N_{HDO} respectively and summed to give ΔG, the observed isotope effect.

Calculation of isotope effect for heat of solution of a salt in H_2O—D_2O *mixtures*

The isotope effect on the heat of solution of sodium chloride in H_2O—D_2O mixtures as a function of a will be calculated and compared with experiment. The calculation will be carried out initially for the heat of solution at infinite dilution, ΔH_s. Values of the isotopic function ΔH_i will be determined using the libration frequencies of the water molecules coordinated to the sodium and chloride ions. These frequencies for the sodium ion are ω_r (635·0 cm^{-1}), ω_r' (459·8 cm^{-1}) and ω_r'' (534·5 cm^{-1}) and for the chloride ion ω_r (598·0 cm^{-1}), ω_r' (432·9 cm^{-1}) and ω_r'' (503·2 cm^{-1}) where the same reduced mass factors previously listed were employed in the calculation of ω_r' and ω_r''. One now calculates

$$\Delta H_i^{Na^+} = -537{\cdot}0N_{D_2O} - 321{\cdot}5N_{HDO}$$

and

$$\Delta H_i^{Cl^-} = -487{\cdot}0N_{D_2O} - 292{\cdot}3N_{HDO}$$

where the units of each are cal mole-ion^{-1}. These expressions for ΔH_i are more general than those given in part I[2] because they now refer to differences between any mixture of light and heavy water and pure light water. The values of ΔH_i and ΔH_s given earlier are for the special case where $N_{D_2O} = 1{\cdot}00$ and $N_{HDO} = N_{H_2O} = 0{\cdot}00$. The isotope effect per mole of salt at infinite dilution is

$$\Delta H_s = \Delta H_s^{Na^+} + \Delta H_s^{Cl^-}$$
$$= 4(\Delta H_i^{Na^+} - \Delta H_w) + 4(\Delta H_i^{Cl^-} - \Delta H_w)$$

The factors of 4 are present to account for the four moles of water which are bound to each mole-ion. The calculated values of ΔH_s are shown in Fig. 2 as curve A, and

the experimental points of Lange and Martin[6] are also given. These authors felt that their data were best represented by a simple linear relationship as indicated by curve C in Fig. 2. The calculated curve lies outside of all the experimental points. The maximum deviation from the straight line approximation is 25 cal mole^{-1} of salt, slightly larger than the reported experimental error of 20 cal mole^{-1} of salt. This simple approach to the problem has, however, resulted in a curve which is in good general agreement with the experimental one. It may well be that the correct form of the

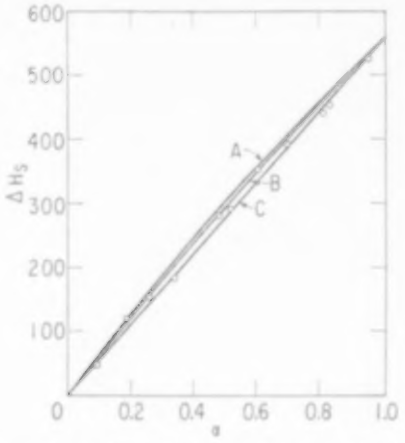

FIG. 2. The isotope effect for the heat of solution of sodium chloride in H_2O—D_2O mixtures at 25° in cal mole^{-1} of salt as a function of the mole fraction of deuterium in the solvent.

curve is slightly convex as indicated by the simple theoretical approach; certainly it is difficult to tell from the experimental data. Better agreement with the experimental results may be obtained by performing a more elaborate calculation, one which takes into account the displacement in the equilibrium brought about by the addition of the ions. This is the substance of the following section.

How does the addition of an ion to an H_2O—D_2O mixture affect the position of the equilibrium respresented by equation (3)? Previous considerations have illustrated that all monatomic singly-charged ions, with the exception of the fluoride ion, are preferentially solvated by light water rather than heavy water. The species HDO will lie somewhere between these waters in its solvating ability.

$$D_2O + X^{\oplus}(H_2O) \rightleftarrows H_2O + X^{\oplus}(D_2O) \qquad K < 1 \tag{5}$$

$$HDO + X^{\oplus}(H_2O) \rightleftarrows H_2O + X^{\oplus}(HDO) \qquad K < 1 \tag{6}$$

Qualitatively, one can see that this fractionation of the water molecules within the solution will decrease the value for the isotope effect for any property connected with ionic solvation. Since the mole fraction of deuterium in the immediate vicinity of the ion is less than that for the solution as a whole, i.e. less than the apparent mole fraction, the actual structure difference is less and isotope effects are correspondingly smaller.

To calculate the integral heat of solution taking into account the displacement in the equilibrium concentrations of the three waters, it is necessary to determine nine

[6] E. Lange and W. Martin, *Z. Physik. Chem.* **A178**, 214 (1936).

water concentrations. These nine concentrations correspond to the mole fractions of the three waters bound to the anions, of the three waters bound to the cations and of the three in the bulk water of the solution. Nine independent relationships may be found between these quantities. The equilibrium constant K_1 of equation (3) is taken as governing the equilibrium between the unbound waters. The equilibrium constants, four in number, corresponding to processes 5 and 6 for both the anion and the cation may be calculated from the theory. The K values are related to one quarter of the ΔF_s values previously tabulated for the ions in Part I.[2] The remaining four relationships are obtained from material balance considerations.

The results of such a calculation are as anticipated. If the apparent mole fraction of deuterium in a H_2O—D_2O mixture α is defined as determined by the total amount of deuterium present in water of all kinds, then α is in every case greater than the value of α_i, the mole fraction of deuterium in the waters bound to the ions and slightly less than the mole fraction of deuterium in the unbound waters. The mole fraction of bound HDO is less than or greater than the mole fraction present in the entire solution depending on whether the mole fraction of deuterium is less than or greater than 0·5. The result of this fractionation is to lower the isotope effect for any value of α from the value calculated for infinite dilution. The values of ΔH_s calculated for a 0·2498m solution (as employed by Lange and Martin[6]) are plotted as curve B in Fig. 2. The calculated points now lie entirely within the experimental error of the data. While the calculated variation in ΔH_s is now closer to the straight line approximation, a definite curvature is still present. The percentage error between the two plots is, however, very small.

Reference should be made to some results obtained by La Mer and Noonan[7] for the integral heat of solution of potassium chloride in mixtures of light and heavy water. Their results show a very slight but definite concave curvature in the plot ΔH_s vs. the mole fraction of deuterium present in the solution. The calculated values for potassium chloride should lie even closer to a straight line than did those for sodium chloride because of the larger fractionation of the water molecules within the solution by potassium ion in comparison with the sodium ion, but still above a straight line. However, their cell involved transfer of the two waters between the two half cells, for which it is difficult to correct. Furthermore, the experimental concavity is very slight and the deviations are therefore still very small.

The behavior of acids in H_2O—D_2O *mixtures*

The addition of an acid to a mixture of light and heavy water results in the formation of four different forms of lyonium ion, H_3O^+, H_2DO^+, HD_2O^+ and D_3O^+, which differ in their protonating ability. Thus, any process, equilibrium or rate, which is a function of acidity will reflect in its own behavior the differences in the acidities of the four species. The problem is further complicated by the differing basicities of the three kinds of water present in a mixture of light and heavy water. Before treating any specific problem, one must be able to determine the equilibrium concentrations of the four lyonium ions for any mole fraction of deuterium present in the solvent.

For a given concentration of lyonium ion in solution (i.e. for a given molar concentration of a strong acid) there are seven equilibrium concentrations which must be determined, those of the three waters and the four forms of lyonium ion. To calculate

[7] V. K. La Mer and E. Noonan, *J. Amer. Chem. Soc.* **61**, 1487 (1939).

these quantities six more relationships are necessary besides the given total concentration of acid. For dilute solutions of the acid, it is possible to employ the same three relationships which were used to determine the concentration of the three waters in pure H_2O–D_2O mixtures (equations 1, 3 and 4). The three remaining expressions are given by the conditions governing the equilibrium between the various forms of lyonium ion and the three waters. The reaction

$$2D_3O^{\oplus} + 3H_2O \rightleftarrows 2H_3O^{\oplus} + 3D_2O \qquad (7)$$

is equivalent to equation 7 of part I[2], and its equilibrium constant (K_2) was evaluated there as 8·200. The equation, as written above, omits the waters necessary for the solvation of the ions. However, it was previously pointed out that hydronium ion leaves the frequencies of the surrounding four water molecules unaffected and therefore the same equilibrium constant is obtained with or without their contribution. In other words there is no free energy of transfer or solvent isotope effect of the "usual kind" for H_3O^+ and D_3O^+. The same will, of course, hold true for the other two lyonium ions in mixtures of light and heavy water. This is equivalent to assuming that the ratio of the activity coefficient of H_3O^+ to that of any of its isotopic isomers is unity and is independent of the mole fraction of deuterium in the solution. This is equivalent to the assumptions made by Nelson and Butler[8] and Schwarzenbach[9] in their treatment of similar problems. However, their reasons for making these assumptions were simply out of necessity, since they possessed no experimental evidence to favor such a procedure. Furthermore, for K_2, Nelson and Butler used the value of 15·3 which is the equilibrium constant for the reaction

$$2D_3O^{\oplus}(D_2O) + 2Cl^{\ominus}(D_2O) + 3H_2O \rightleftarrows 2H_3O^{\oplus}(H_2O) + 2Cl^{\ominus}(H_2O) + 3D_2O$$

i.e. they were not able to allow for the free energy of transfer of the chloride ion and hence could not determine the value of K_2 (8·2) employed in the present calculations. Purlee[10] used a value of K_2 of 11·0 to obtain an improved fit to the pertinent experimental data. To arrive at this value he calculated that the free energy of transfer of chloride ion from H_2O to D_2O is $-\frac{1}{2}RT \ln (11{\cdot}0/17{\cdot}4) = 140$ cal mole^{-1} from e.m.f. measurements of Schwarzenbach on liquid junction cells by assuming equal liquid junction potentials between HCl solutions in either H_2O or D_2O vs. a saturated KCl solution in H_2O. This correction is in the right direction, but is less than our calculated value of $\Delta F_s = 233$ cal mole^{-1}, which is free from this dubious use of liquid junction cells and these assumptions about liquid junction potentials.

In order to calculate the equilibrium concentrations of the species H_2DO^+ and HD_2O^+ it is necessary to determine their partition function ratios. These cannot be calculated directly since their spectra cannot be observed. However, a very reasonable assumption may be made, equivalent to one used earlier by Schwarzenbach[9]. The assumption is

$$Q_{H_2DO^+}/3Q_{H_3O^+} = 3Q_{D_3O^+}/Q_{HD_2O^+} = Q_{HD_2O^+}/Q_{H_2DO^+}$$

where each Q_i is a partition function. This application of the rule of the geometric

[8] J. C. Hornel and J. A. V. Butler, *J. Chem. Soc.* 1361 (1936); W. J. C. Orr and J. A. V. Butler, *Ibid.* 330 (1937); W. E. Nelson and J. A. V. Butler, *Ibid.* 957 (1938).
[9] G. Schwarzenbach, *Z. Electrochem.* **44**, 46 (1938).
[10] E. L. Purlee, *J. Amer. Chem. Soc.* **81**, 263 (1959).

mean[4] is equivalent to assuming that progressive substitution of deuterium for hydrogen in hydronium ion brings about equal stepwise increments in thermodynamic differences. In effect, each HO bond is considered as an independent entity in the sense that the HO bond of HD_2O^+ is considered to have the same fundamental frequencies as an HO bond in H_3O^+. The factors of three take into account the different statistical probabilities of the species, i.e. the species H_3O^+ and D_3O^+ possess symmetry numbers of three while the symmetry numbers of H_2DO^+ and HD_2O^+ are unity. The symmetry number is the number of indistinguishable orientations obtainable by rotation of the molecule and is a divisor reducing the partition functions. The partition function ratio $Q_{D_3O^+}/Q_{H_3O^+}$ may be calculated from the value of K_2 and the calculated value of the partition function ratio of light and heavy water.[2]

$$Q_{D_2O}/Q_{H_2O} = 1437$$

$$Q_{D_3O^+}/Q_{H_3O^+} = 19023$$

From this value and the above relationships the other ratios are

$$Q_{HD_2O^+}/Q_{H_2DO^+} = 26{\cdot}70$$

$$Q_{H_2DO^+}/Q_{H_3O^+} = 80{\cdot}08$$

$$Q_{D_3O^+}/Q_{HD_2O^+} = 8{\cdot}898$$

Two more equilibria may now be written which involve the species H_2DO^+ and HD_2O^+ and their equilibrium constants calculated.

$$H_2O + H_2DO^+ \rightleftarrows HDO + H_3O^+ \qquad K_3 = 0{\cdot}9420 \tag{8}$$

$$H_2O + D_3O^+ \rightleftarrows HDO + HD_2O^+ \qquad K_4 = 8{\cdot}478 \tag{9}$$

According to the assumptions made above concerning the two intermediate forms of lyonium ion, the constants K_3 and K_4 should, aside from statistical factors, be of equal magnitude. Therefore $K_4/6$ should equal $3K_3/2$, as indeed it does.

These relationships enable one to calculate the ratios

$$[H_3O^+]/[D_3O^+] = K_2^{1/2}([H_2O]/[D_2O])^{3/2} = 1/\lambda_1$$

$$[H_3O^+]/[H_2DO^+] = K_3[H_2O]/[HDO] = 1/\lambda_2$$

$$[HD_2O^+]/[D_3O^+] = K_4[H_2O]/[HDO] = \lambda_3/\lambda_1$$

If the total lyonium ion concentration is denoted by $[L_3O^+]$, then

$$[L_3O^+] = (1 + \lambda_1 + \lambda_2 + \lambda_3)[H_3O^+] = \lambda[H_3O^+];$$

$$\lambda = 1 + \frac{[D_2G]^{3/2}}{K_2^{1/2}[H_2O]^{3/2}} + \frac{[HDO]}{K_3[H_2O]} + \frac{K_4[D_2O]^{3/2}}{K_2^{1/2}[HDO][H_2O]^{1/2}} \tag{10}$$

The units of concentration are moles in a fixed number of moles (e.g. 55·5) of solvent. The four lyonium ion concentrations may be calculated for any value of the deuterium content of the solution and any total lyonium ion concentration. The ratios of the lyonium ion concentrations are fixed by the above four equilibrium constants and independent of any other processes occurring in the solution.

A strong acid in a mixture of H_2O and D_2O is completely dissociated into its conjugate base and the four different types of lyonium ions. If, for convenience, the total acid concentration $[L_3O^+]$ $(= [H_3O^+] + [H_2DO^+] + [HD_2O^+] + D_3O^+])$ is taken as unity, all four lyonium ion concentrations may be calculated for varying mole fractions of deuterium. The results of such a calculation are illustrated in Fig. 3. The most important feature of this plot is the lack of symmetry, which is a direct consequence of the differing acidities of the four lyonium ions. The progressive substitution of deuterium for hydrogen increases the acidity of the ion with the result that the ratio

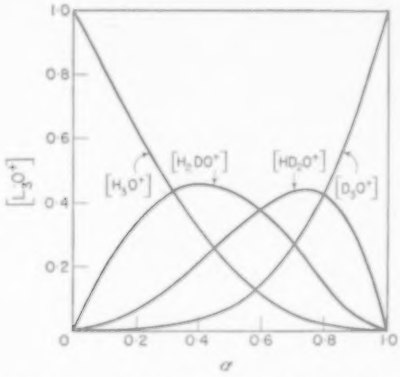

FIG. 3. The lyonium ion concentrations for a strong acid in H_2O—D_2O mixtures at 25° where total acid concentration $[L_3O^+] = 1{\cdot}00$.

of D/H is greater in the solvent than in the ions. When the mole fraction of deuterium in the solvent is 0·50, the mole fraction of deuterium in the ions is only 0·41; similarly for a solvent deuterium mole fraction of 0·90, the deuterium mole fraction in the ions is 0·87. The OH bond strength is greater for water than for the ion. The zero-point energy is thus greater for water than for the ion and thus the deuterium should concentrate in the water as found.

Calculation of ionization constants of weak acids in H_2O—D_2O *mixtures*

To test the assumptions made in the above analysis, the dissociation constant of a weak acid in mixtures of light and heavy water will be calculated and the values obtained compared with experimentally determined ones.

Other acids than lyonium ion are generally dissociated to a greater extent in light water than is the deuterated form of the acid in heavy water.

$$HA + H_2O \rightleftarrows H_3O^{\oplus} + A^{\ominus} \qquad K_{HA}$$

$$DA + D_2O \rightleftarrows D_3O^{\oplus} + A^{\ominus} \qquad K_{DA}$$

One reason why the ratio K_{HA}/K_{DA} possesses a value greater than unity is the fact that deuteronium ion is a stronger acid than hydronium ion. The other determining factor is the strength of the acid HA. The weaker this acid is, the stronger is the HA bond and thus the greater the zero-point energy difference between the acid and its deuterated form. Therefore, the lower the acidity possessed by HA, the greater will be the tendency for the deuterium to concentrate in the undissociated form of the acid.

This effect enhances the former one with the result that K_{HA}/K_{DA} should increase as the acidity of HA is decreased.

Dissolving a weak acid in a mixture of light and heavy water establishes equilibria between HA, DA and all four different lyonium ions. The dissociation constant in a mixture of deuterium mole fraction α is

$$K_\alpha = \frac{[L_3O^+][A^-]\gamma_{L_2O^+}\gamma_{A^-}}{[LA][L_2O]\gamma_{LA}\gamma_{L_2O}}$$

where [LA] = [HA] + [DA], $[L_2O] = [H_2O] + [HDO] + [D_2O]$, and each γ is an activity coefficient. Combining equations for K_α, K_{HA} and K_{DA} gives

$$\frac{K_{HA}}{K_\alpha} = \frac{[H_3O^+][L_2O]\gamma_{H_2O^+}\gamma_{L_2O}}{[L_3O^+][H_2O]\gamma_{L_2O^+}\gamma_{H_2O}} + \frac{K_{HA}[D_3O^+][L_2O]\gamma_{D_2O^+}\gamma_{L_2O}}{K_{DA}[L_3O^+][D_2O]\gamma_{L_2O^+}\gamma_{D_2O}} \qquad (11)$$

where all concentrations and activity coefficients refer to a mixture of deuterium mole

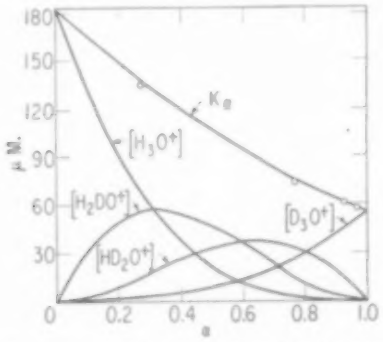

FIG. 4. The dissociation constant of acetic acid and the hydronium ion concentrations in H_2O—D_2O mixtures at 25° in micromolar units where $K_\alpha = [L_3O^+]$.

fraction α. Since H_2O, HDO and D_2O form ideal solutions, $\gamma_{H_2O} = \gamma_{D_2O} = \gamma_{L_2O}$ in any mixture. Since lyonium ions leave the structure of water undisturbed, $\gamma_{H_3O^+} = \gamma_{D_3O^+} = \gamma_{L_3O^+}$ in any mixture. Therefore the activity coefficient ratios in equation 11 are unity. The concentration ratios $[H_2O]/[L_2O]$ and $[D_2O]/[L_2O]$ can be calculated from K_1 (equations 1, 3 and 4); likewise $[H_3O^+]/[L_3O^+]$ and $[D_3O^+]/[L_3O^+]$ can be calculated from K_2, K_3 and K_4 (equations 7–10). Therefore K_{HA}/K_α and hence K_α can be calculated for any deuterium mole fraction α. Fig. 4 shows the calculated results for 0·02 M stoichiometric acid concentration ([LA] + $[L_3O^+]$).

La Mer and Chittum[11] have determined K_{HA}, K_{DA} and a number of K_α values for acetic acid in 0·02 M stoichiometric concentration by a conductivity method. Their values of K_{HA} and K_{DA} are $1{\cdot}84 \times 10^{-5}$ and $0{\cdot}555 \times 10^{-5}$ respectively. By convention $[H_2O]\gamma_{H_2O}$, $[D_2O]\gamma_{D_2O}$ and $[L_2O]\gamma_{L_2O}$ are set equal to unity. Also γ_{A^-}/γ_{HA} was assumed to be independent of α. This is reasonable because A^- and HA are of similar size and the charge on A^- is on oxygen, just as in hydroxide ion, which is known to leave the structure of water undisturbed.[2] The agreement between the calculated results (line) and experimental results (circles) in Fig. 4 is excellent. The pronounced dip in the value of K_α as noted by La Mer and Chittum is predicted by the calculations.

[11] V. K. La Mer and J. P. Chittum, *J. Amer. Chem. Soc.* **58**, 1642 (1936).

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Their results show a maximum deviation from linearity of −12 per cent and the calculated ones give a value of −11 per cent. The good agreement between the experimental and calculated results provides an *a posteriori* proof of the assumptions made in calculating the partition function ratios for the species H_2DO^+ and HD_2O^+. Fig. 4 also illustrates the variations in the concentrations of the four lyonium ions for acetic acid where $K_\alpha = [L_3O^+]$, i.e. when $[A^-] = [LA]$.

Acid-catalyzed reactions in mixtures of light and heavy water. As first noted by Gross[12] and later elaborated by Butler[8] and Purlee[10], a study of the variation in the rate of an acid-catalyzed reaction as a function of the deuterium content of the solvent may allow one to differentiate between possible reaction mechanisms.

First consider a mechanism in which the substrate S reacts with acids via a transition state of composition $(SH^+)^*$, i.e. one not containing the elements of any additional solvent molecule or base. The rate of such a reaction is proportional to the concentration of the protonated transition state $[SH^+]^*$.

Among other possible mechanisms for an acid-catalyzed reaction are ones in which the transition state has the composition $(SHX)^*$ (as it might if the proton transfer from the acid HX were rate determining) or $(XSH)^*$ (as it might for a slow reaction of a base X^- with SH^+). The rate is then dependent on the nature of X.

For the first transition state $(SH^+)^*$, the isotope effect can be calculated as a function of α (the mole fraction of deuterium) as shown below. If instead the transition state is $(SHX)^*$ or $(XSH)^*$, the isotope effect need not follow this calculated dependence on α. The present calculations are based entirely upon the results that have been obtained by the use of the present theory. In a mixture of light and heavy water there will be a second term in the rate expression proportional to the concentration of the deuterated transition state $[SD^+]^*$. The two transition states are in equilibrium with all four kinds of lyonium ions. However, these equilibria are not all independent, and it is sufficient for the present purpose to consider only two.

$$H_3O^+ + S \rightleftarrows SH^{+*} + H_2O \qquad K_H^*$$

$$D_3O^+ + S \rightleftarrows SD^{+*} + D_2O \qquad K_D^*$$

The ratio of the ordinary experimental first-order rate constant in a mixture of H_4O and D_4O to that in H_4O is

$$\frac{k_\alpha}{k_H} = \frac{[SH^+]_\alpha^*}{[SH^+]_H^*} + \frac{[SD^+]_\alpha^*}{[SH^+]_H^*}$$

where the starred concentrations are effective concentrations, which, like the K^* constants, include the effective mass for crossing the barrier. Hence

$$\frac{k_\alpha}{k_H} = \frac{[H_3O^+]_\alpha[H_2O]_H(\gamma'_{H_3O^+})_\alpha(\gamma'_{H_2O})_H(\gamma_S)_\alpha(\gamma^*_{SH^+})_H}{[H_3O^+]_H[H_2O]_\alpha(\gamma'_{H_3O^+})_H(\gamma'_{H_2O})_\alpha(\gamma_S)_H(\gamma^*_{SH^+})_\alpha}$$

$$+ \frac{k_D[D_3O^+]_\alpha[D_2O]_D(\gamma'_{D_3O^+})_\alpha(\gamma'_{D_2O})_D(\gamma_S)_\alpha(\gamma^*_{SD^+})_D}{k_H[D_3O^+]_D[D_2O]_\alpha(\gamma'_{D_3O^+})_D(\gamma'_{D_2O})_\alpha(\gamma_S)_D(\gamma^*_{SD^+})_\alpha} \qquad (12)$$

The ratios of activity coefficients may be set equal to unity for the following reasons.

[12] P. Gross, H. Steiner and F. Krauss, *Trans. Faraday Soc.* **32**, 877 (1936); P. Gross and A. Wischin, *Ibid.* **32**, 879 (1936); P. Gross, H. Steiner and H. Suess, *Ibid.* **32**, 883 (1936).

Since H_2O, D_2O and HDO form ideal solutions, $(\gamma_{H_2O})_x = (\gamma_{H_2O})_H$ and $(\gamma_{D_2O})_x = (\gamma_{D_2O})_D$. Since H_3O^+ and D_3O^+ do not change the structure of water[2], $(\gamma_{H_3O^+})_x = (\gamma_{H_3O^+})_H$ and $(\gamma_{D_3O^+})_x = (\gamma_{D_3O^+})_D$. The remaining assumptions that $(\gamma^*_{SH^+})_x/(\gamma^*_{SH^+})_H = (\gamma_S)_x/(\gamma_S)_H$ and $(\gamma^*_{SD^+})_x/(\gamma^*_{SD^+})_D = (\gamma_S)_x/(\gamma_S)_D$ are equivalent to assuming that solvation of the transition state changes in the same way with α as solvation of the ground state of S. If the transition state and S are large they both will cause considerable breakdown of the structure of water, and more as α increases because D_2O has the most structure to start with. However, such changes with α should be practically the same because of the closely similar sizes of $SH^{+\bullet}$ and S. There might be a difference associated with the electrical effect of protonating one atom in S. However, a transition state like protonated ethylene oxide, for example, probably would have hydrogen bonds between the proton and H_2O and between the remaining unshared pair and H_2O quite similar to hydrogen bonds formed by H_3O^+ or H_2O, already shown to be unaffected by α. Therefore at least in this case there is reason to expect the electrical contribution likewise to be unaffected by α. With these assumptions[13]

$$\frac{k_x}{k_H} = g_H + \frac{k_D}{k_H} g_D \tag{13}$$

where $$g_H = \frac{[H_3O^+]_x[H_2O]_H}{[H_3O^+]_H[H_2O]_x}, \qquad g_D = \frac{[D_3O^+]_x[D_2O]_D}{[D_3O^+]_D[D_2O]_x}$$

A knowledge of the isotope effect k_D/k_H for the reaction in question together with the

[13] This last assumption seems to be the weakest one and may not be valid for all substrates. The success of equation (13) is probably the best test of its validity.

Previous authors[5,10,12] have assumed instead that $\gamma_{H_2O^+}/\gamma^*_{SH^+}$ is independent of α. This is *not* valid. Although $\gamma_{H_2O^+}$ is independent of α because H_3O^+ does not change the structure of water, it is certainly untrue that γ_{SH^+} is independent of α except fortuitously, since large ions in general break down the structure of water.[2]

Alternatively one can write all lyon equilibria in terms of H^+ and D^+ instead of H_3O^+, H_2DO^+, HD_2O^+ and D_3O^+.[14] Substituting into equation (12) from the equilibria

$$H^+ \text{ (solvated)} + H_2O \text{ (solvated)} \rightleftharpoons H_3O^+ \text{ (solvated)}$$

$$D^+ \text{ (solvated)} + D_2O \text{ (solvated)} \rightleftharpoons D_3O^+ \text{ (solvated)}$$

yields the seemingly somewhat simpler equation

$$\frac{k_x}{k_H} = \frac{[H^+]_x(\gamma_{H^+})_x(\gamma_S)_x(\gamma^*_{SH^+})_H}{[H^+]_H(\gamma_{H^+})_H(\gamma_S)_H(\gamma^*_{SH^+})_x} + \frac{k_D[D^+]_x(\gamma_{D^+})_x(\gamma_S)_x(\gamma^*_{SD^+})_D}{k_H[D^+]_H(\gamma_{D^+})_H(\gamma_S)_H(\gamma^*_{SD^+})_x}$$

However, in comparing this equation with experiment it is *not* valid to assume that $(\gamma_{H^+})_x = (\gamma_{H^+})_H$ or that $(\gamma_{D^+})_x = (\gamma_{D^+})_D$, because H^+ is smaller than Li^+ and so should increase the structure of water, since large ions like Na^+ and Cl^- decrease the structure of water, H_3O^+ and Li^+ leave it unchanged and the small fluoride ion increases it[2] (i.e. $(\gamma_{Na^+})_x > (\gamma_{Na^+})_H$, $(\gamma_{Cl^-})_x > (\gamma_{Cl^-})_H$, $(\gamma_{H_3O^+})_x = (\gamma_{H_3O^+})_H$, $(\gamma_{Li^+})_x = (\gamma_{Li^+})_H$ and $(\gamma_{F^-})_x < (\gamma_{F^-})_H$ for $\alpha \neq 0{\cdot}00$). Instead $(\gamma_{H^+})_x/(\gamma_{H^+})_H$ and $(\gamma_{D^+})_x/(\gamma_{D^+})_D$ must be calculated as functions of α. For example

$$\frac{[H_3O^+]_x(\gamma_{H_3O^+})_x}{[H_2O]_x(\gamma_{H_2O})_x[H^+]_x(\gamma_{H^+})_x} = K_x$$

and

$$\frac{[H_3O^+]_x[H_2O]_H[H^+]_H(\gamma_{H_3O^+})_x(\gamma_{H_2O})_H(\gamma_{H^+})_H}{[H_2O]_x[H_2O^+]_H[H^+]_x(\gamma_{H_3O^+})_H(\gamma_{H_2O})_x(\gamma_{H^+})_x} = 1$$

Therefore

$$\frac{(\gamma_{H^+})_x}{(\gamma_{H^+})_H} = \frac{[H_3O^+]_x[H_2O]_H[H^+]_H(\gamma_{H_3O^+})_x(\gamma_{H_2O})_H}{[H_2O]_x[H_2O^+]_H[H^+]_x(\gamma_{H_3O^+})_H(\gamma_{H_2O})_x}$$

This shows that the ratio $(\gamma_{H^+})_x/(\gamma_{H^+})_H$ is not unity and is a function of α. Indeed substitution of this ratio and the similar expression for $(\gamma_{D^+})_x/(\gamma_{D^+})_D$ into the above equation for k_x/k_H again gives equation (12).

[14] F. A. Long, private communication.

variations in g_H and g_D allows one to predict k_a/k_H for various a. Agreement of the calculated values of k_a/k_H with experiment is evidence that the transition state is $(SH^+)^*$ rather than $(SHX)^*$ where X is water or any other base.

TABLE 1. VARIATIONS IN THE GROSS EQUATION PARAMETERS IN H_2O—D_2O MIXTURES AT 25°

a	N_{D_2O}	N_{HDO}	g_H	g_D
0·000	0·0000	0·0000	1·0000	0·0000
0·100	0·0101	0·1798	0·9839	0·0383
0·250	0·0628	0·3743	0·9425	0·1100
0·400	0·1606	0·4788	0·8732	0·2035
0·500	0·2506	0·4987	0·8062	0·2815
0·600	0·3606	0·4788	0·7174	0·3754
0·750	0·5628	0·3743	0·5303	0·5541
0·900	0·8101	0·1798	0·2544	0·7961
1·000	1·0000	0·0000	0·0000	1·0000

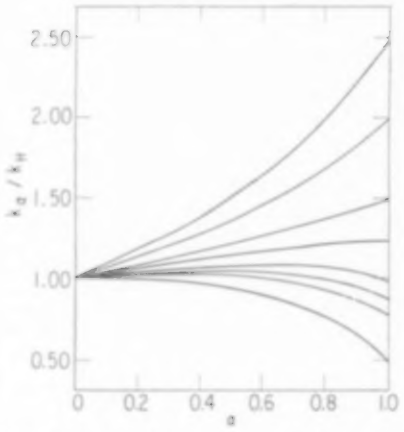

FIG. 5. The predicted variations in the rate ratio k_a/k_H for a number of values of the isotope effect k_D/k_H for acid catalyzed reactions involving specific hydrogen-ion catalysis at 25°.

Values of g_H and g_D for selected values of a are listed in Table 1. They are simply ratios of concentrations of H_2O, D_2O, H_3O^+ and D_3O^+ as defined under equation (13). These concentrations were calculated previously in the section entitled *The behavior of acids in* H_2O—D_2O *mixtures*. Fig. 5 illustrates the variation in k_a/k_H for a number k_D/k_H values.

The agreement of calculation with experiment was shown for a number of reactions by Purlee[10] using a K_2 of 11·0. The agreement is similar with our K_2 of 8·2. Both fit better than the value of 15·3 used by Nelson and Butler[8].

Tetrahedron, 1960, Vol. 10, pp. 212 to 214. Pergamon Press Ltd. Printed in Northern Ireland

HYBRIDIZATION IN CARBON MONOXIDE

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(*Received* 8 *February* 1960)

Abstract—Qualitative molecular orbital descriptions of N_2 and CO are given and compared, with special emphasis on hybridization of *s* and *pσ* orbitals. The principle that orbitals combining to form a strong bond must have comparable energies makes it likely that the atomic orbital of carbon involved in the σ bond in CO has predominantly *s* character, and leads to a lone pair on carbon with predominant *p* character. These arguments lead to a straightforward interpretation of the chemical properties of CO and N_2, and are in agreement with conclusions implied in, but not specifically brought out by more elaborate MO treatments.

THE isoelectronic molecules, nitrogen and carbon monoxide, have strikingly similar physical properties, yet a myriad of reactions are possible with the latter[1] while the homonuclear nitrogen is essentially inert. In molecular orbital theory, the ten valence electrons of each compound are represented by the configuration $(1\sigma)^2(2\sigma)^2(3\sigma)^2\pi^4$, which is consistent with the presence of lone pair electrons on each of the atoms of both molecules, and a triple bond between the joined atoms. Careful molecular orbital calculations are available for both molecules,[2,3] and the difference in their behavior is interpretable from these complete treatments. However, the difference can very readily be illustrated by means of energy level diagrams constructed on the basis of a much simpler, qualitative molecular orbital discussion, with special emphasis on hybridization; the conclusions will be shown to be in agreement with those from the more exact quantitative treatment.

In the case of nitrogen, the symmetry of the molecule requires that each MO be symmetrical, i.e. made up of equal contributions from the two atoms. The energy level diagrams for the isolated atoms are given at the extreme right and left in Fig. 1(a). In the cylindrical field of the molecule, the p_z and *s* orbitals of each of the nitrogen atoms (calling the bond axis the *z* axis) belong to the same symmetry species and can accordingly be mixed (hybridized). The hybridization leads to an energy level scheme in which each atom has two π orbitals and two σ orbitals, as shown in the second and fourth columns in Fig. 1(A). The σ orbitals can be represented by $\sigma_1 = s\cos\alpha + p_z\sin\alpha$ and $\sigma_2 = s\sin\alpha - p_z\cos\alpha$. The value of α can only be determined by a minimization of the total energy of the molecule but qualitative conclusions can be drawn without detailed calculations.

The hybridization of the *s* and one *p* orbitals results in two new levels, one (σ_2) below the *p* level of the isolated atom and one (σ_1) above the *s* level of the isolated atom. The admixture of the *s* orbital to the p_z orbital greatly increases the bonding power of σ_2 but is accompanied by a corresponding admixture of *p* character to the *s* orbital to form σ_1. Since σ_1 contains two electrons, and σ_2 only one, this hybridization involves a net expenditure of energy equivalent to the promotion of the appropriate

[1] M. Orchin and I. Wender, *Catalysis* (Edited by P. H. Emmett), Vol. V. Reinhold, New York (1957).
[2] C. W. Scherr, *J. Chem. Phys.* **23**, 569 (1955).
[3] R. S. Sahni, *Trans. Faraday Soc.* **49**, 1246 (1953).

fraction of one electron from an s to a p orbital. Experience teaches that, in the words of Mulliken, "a little hybridization goes a long way", so that only a small admixture of s character greatly increases the bonding power of σ_2, and at the same time involves not too great an expenditure of promotion energy. Consequently it can be concluded that σ_2 will be predominantly a p_z orbital with some admixture of s character, and conversely, σ_1 will be predominantly an s orbital with some admixture of p_z character.

In the case of carbon monoxide, since the atomic orbitals of the two atoms which

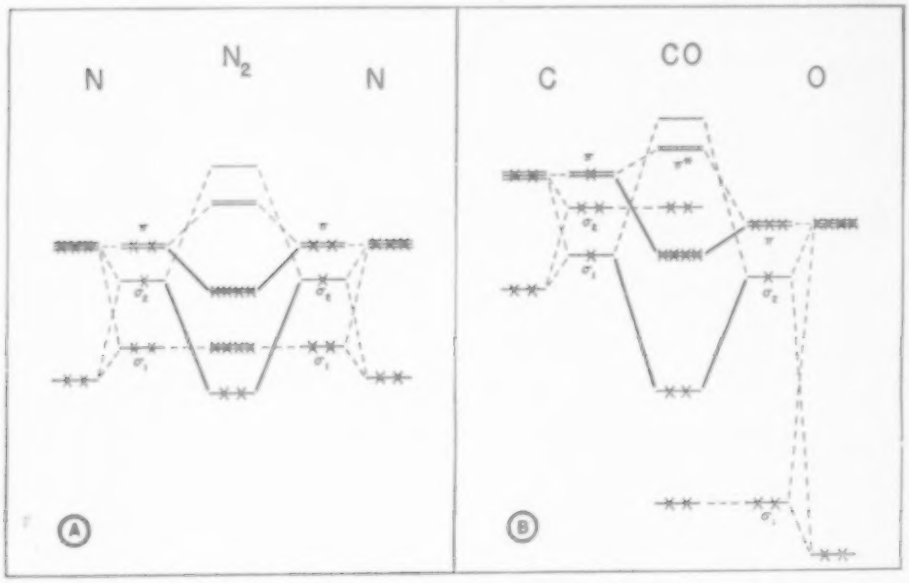

FIG. 1. Energy level diagrams for (A) N_2 and (B) CO.

form the sigma bond need not be equivalent, their relative energies must also be considered. It is well-known that two atomic orbitals form a strong bond only if their energies are fairly close. Inspection of Fig. 1(B), which gives the energy level diagram, shows that this criterion of similar energies in CO can only be met if σ_1 of carbon interacts with σ_2 of oxygen to form the sigma bond. As a result, the lone pair of the carbon atom in :C≡O: will be in a σ_2 oribital and have largely p_z character and the lone pair of the oxygen atom will be in σ_1, and have largely s character.[4] The ionization potential of the carbon lone pair is thus quite low, making it a relatively basic lone pair. This relatively high energy level of the lone pair and the fact that it is largely p in character and thus strongly directional must be responsible for the many reactions in which carbon monoxide acts as a nucleophile. The ionization potential of the oxygen lone pair is relatively high and these electrons are thus unavailable chemically; further, the orbital has predominantly s character, and is accordingly not strongly directional. The lone pair electrons on the nitrogen atoms in N_2 are similar to those of the oxygen atom in CO. These facts explain why the reactivity

[4] This assignment is diametrically opposite to that made by W. Moffitt, *Proc. Roy. Soc.* A **196,** 524 (1949) who assumed that the orbital involved in forming the σ bond is essentially sp^3 hybridized, and hence the orbital containing the lone pair on carbon has 75 per cent s character.

of carbon monoxide resides on the carbon atom and is so much greater than that of nitrogen.

The energy level diagram of CO further serves to explain the reactivity of carbon monoxide toward nucleophilic reagents (e.g. RO^-) as well as the unusual ability of carbon monoxide to accept back-donation from filled d orbitals in transition metal carbonyls. The lowest unoccupied orbital is a π^* orbital ($c_C p\pi_C - c_O p\pi_O$). Inspection of the MO diagram shows that this orbital lies much closer to the $p\pi$ orbitals of the isolated carbon atom than those of the isolated oxygen atom, and hence receives a predominant contribution from the carbon $p\pi$ orbital and a much smaller contribution from the corresponding oxygen orbital, i.e. $c_C > c_O$. Accordingly, nucleophilic attack occurs exclusively on carbon, and overlap of the π^* orbital with a $d\pi$ orbital of a metal is favorable because in the $\int d\pi_{Metal}\pi_{CO}^*\, d\tau = \int d\pi_{Metal}(c_C p\pi_C - c_O p\pi_O)\, d\tau = c_C \int d\pi_{Metal}\, p\pi_C\, d\tau - c_O \int d\pi_{Metal}\, p\pi_O d\tau$ the last integral is small and multiplied by a small coefficient, and $\int d\pi_{Metal}\, p\pi_C d\tau$ is large and multiplied by a large coefficient. The relatively low energy of the π^* orbital further contributes to its acceptor ability and electrophilic character.

To test these qualitative conclusions using the data available for these molecules,[2,3] it is necessary to transform the non-localized orbitals into equivalent or localized orbitals. Unfortunately this transformation involves some arbitrary decisions and considerable calculation and consequently only rough approximations will be used here. Sahni has transformed his orbitals of CO into a set of "localized" orbitals.[3] From his data it can be estimated that the lone pair orbital localized predominantly on the oxygen atom has about 22 per cent p character and the orbital localized predominantly on carbon approximately 68 per cent p character. An approximate transformation of Scherr's $3\sigma_g$ and $2\sigma_u$ orbitals leads to equivalent, largely localized, but non-orthogonal orbitals corresponding roughly to the two nitrogen lone pairs. At the nitrogen atom on which each of these equivalent orbitals is predominantly localized, the orbital has approximately 29 per cent p character. Thus the qualitative conclusions regarding hybridization shown in Fig. 1 are borne out by use of the more quantitative calculations in the literature.

A further difference between nitrogen and carbon monoxide is that, upon ionization, the bond strength and internuclear distance in the former decreases whereas in CO both increase.[5] The schematic energy level diagram for N_2 in Fig. 1(A), in which the highest occupied orbital is a bonding π-orbital is consistent with the observed bond-weakening effect of ionization. However, Scherr's calculations which take account of interaction of all σ orbitals show that the highest occupied orbital is one of the lone pair orbitals ($3\sigma_g$). Only on the basis of quantitative calculations could one decide whether in N_2^+ the sequence of levels would be retained or whether the π-level would lie above $3\sigma_g$. The schematic diagram of Fig. 1(B) for CO has the lone pair orbital of carbon as the highest occupied orbital and hence removal of an electron would not lead to any bond-weakening. Furthermore, ionization, which according to Fig. 1(B) occurs essentially at the carbon atom would increase the electron affinity of this atom and hence lower its energy levels and permit a more even distribution of the bonding π electrons between C and O, thereby strengthening the bond.

Acknowledgement—The authors wish to thank the Office of Ordnance Research, U.S. Army, for support of this work.

[5] L. H. Long and A. D. Walsh, *Trans. Faraday Soc.* **43**, 342 (1947).

Tetrahedron, 1960, Vol. 10, pp. 215 to 222. Pergamon Press Ltd. Printed in Northern Ireland

VOL. 10 1960

SYNTHESIS OF HETEROCYCLIC STEROIDS—III*

AN UNSUCCESSFUL ATTEMPT AT THE SYNTHESIS OF B-NOR-6-THIAEQUILENIN THROUGH 3-CYANO-7-METHOXY-4-OXO-1,2,3,4-TETRAHYDRODIBENZOTHIOPHENE

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(*Received* 31 *March* 1960)

Abstract—The synthesis of 3-cyano-7-methoxy-3-methyl-4-oxo-1,2,3,4-tetrahydrodibenzothiophene is described. The latter could not be converted to B-nor-6-thiaequilenin, the thioster of equilenin since it failed to undergo Stobbe Condensation with diethyl succinate.

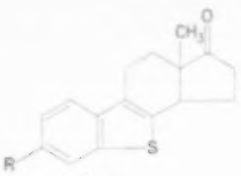
Work is in progress on the *total* synthesis of heterocyclic steroids wherein the hetero atom forms a part of the cyclopenta-(a)-phenanthrene unit, and where the essential structural features associated with the steroidal molecules, such as the angular methyl group, the oxygen functions and the particular stereochemical pattern have been retained in the relevant positions. The steroidal alkaloids are representatives of the heterocyclic steroids, but in these cases the hetero element is not a part of the C_{17} steroidal skeleton.

The phenolic estrogenic steroids were chosen as starting materials owing to their carcinogenic activity and aromaticity which reduces the number of possible stereoisomers. The phenanthrene-bridge position in the steroids was replaced by the hetero atom by substituting the B-ring by the thiophene, furan and pyrrole rings.

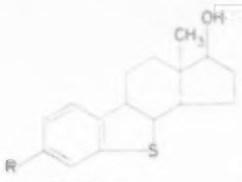
Among the sulphur containing compounds, thiapyrano steroids[1] of ambiguous structure and the total synthesis of the thiopheno analogues of 3-desoxyequilenin (I)[2,3,5] and 3-desoxyisoestradiol (II)[4] have been reported. The present paper records an unsuccessful attempt to synthesize B-nor-6-thiaequilenin (Ia). In parts IV and V of this series, the work on furano and pyrrolo steroids will be described, although preliminary reports on the synthesis of furano-steroids[6] and aza-steroids[7] have already been published.

* Part II, Reference 4.

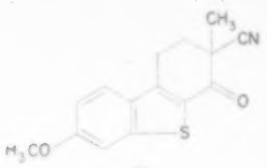
[1] I. N. Nazarov, I. A. Gurvich and A. I. Kuznetsova, *Chem. Abstr.* **47**, 7520 (1953); **49**, 2456 (1955).
[2] R. B. Mitra and B. D. Tilak, *J. Sci. Ind. Res. India* **14B**, 132 (1955).
[3] R. B. Mitra and B. D. Tilak, *J. Sci. Ind. Res. India* **15B**, 497 (1956).
[4] R. B. Mitra and B. D. Tilak, *J. Sci. Ind. Res. India* **15B**, 573 (1956).
[5] R. J. Collins and E. V. Brown, *J. Amer. Chem. Soc.* **79**, 1103 (1957). Collins and Brown have wrongly concluded that "the paper by R. B. Mitra and B. D. Tilak reaches the same conclusions as our work, except that the 154·5° melting reduction product is reported to be the thiophene analogue of 3-desoxyequilenin". We, did not report the compound m.p. 154·5°, which Collins and Brown obtained in the hydrogenation of dehydrothiaequilenin, but obtained I in two isomeric forms m.p. 90–92° and m.p. 146–148°. The two compounds gave almost identical U.V. spectra which were very similar to that of 1,2,3,4-tetrahydrodibenzothiophene, and differed markedly from the spectrum of dehydrothiaequilenin, m.p. 172·5–174°. Compound, m.p. 154·5° obtained by Collins and Brown gave a U.V. spectrum similar to that of dehydrothiaequilenin, and they concluded that the two were polymorphic forms of the same compound. Since the compound m.p. 146–148° gave a spectrum identical with I m.p. 90–92°, and very different from dehydrothiaequilenin, the compound cannot be an impure sample of that m.p. 154·5°, a conclusion which Collins and Brown's comments appear to suggest.
[6] G. V. Bhide, N. L. Tikotkar and B. D. Tilak, *Chem. & Ind.* 1319 (1957).
[7] G. V. Bhide, N. R. Pai, N. L. Tikotkar and B. D. Tilak, *Tetrahedron* **4**, 420 (1958).



I, R = H
I a, R = OH

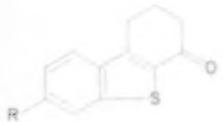


II, R = H
II a R = OH

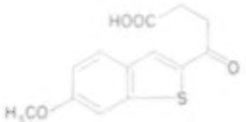


III

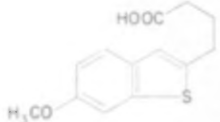
In the synthesis of the equilenin thioster (Ia) the synthesis of 7-methoxy-4-oxo-1,2,3,4-tetrahydrodibenzothiophene (IV) by succinoylation of 6-methoxythionaphthene was first attempted in view of the synthesis[3] of V from thionaphthene. As in the preparation of 6-methoxythionaphthene by cyclization of ω-dimethoxyethyl *m*-methoxyphenyl sulphide[8] a 4-substituted derivative could also be formed, it was necessary to establish the homogeneity and identity of 6-methoxythionaphthene prepared. Demethylation of the latter gave the known 6-hydroxythionaphthene[9] and no 4-hydroxythionaphthene.[10] Unlike the orientation in thionaphthene, where electrophilic substitution usually gives a mixture of 3- and 2-substituted derivatives with the former predominating, Friedel–Crafts' inte action of 6-methoxythionaphthene and β-carbomethoxypropionyl chloride gave a mixture of compounds which contained (proved later), the undesired methyl β-(6-methoxy-2-thionaphthenoyl)-propionate (VI) as the major constituent. The formation of the latter is due to the strong mesomeric effect of the methoxy group leading to higher reactivity at the 2-position. β-Methoxynaphthalene, an isoster of 6-methoxythianaphthene, also behaves similarly in Friedel–Crafts' substitutions.[11]



IV, R = OCH_3
V, R = H



VI



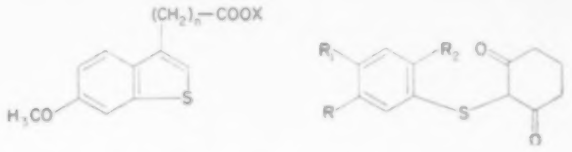
VII

Martin–Clemmensen reduction of VI gave γ-(6-methoxy-2-thionaphthenyl)-butyric acid (VII), but from the Wolff–Kishner–Huang-Minlon reduction no pure compound could be isolated. That the succinoylation of 6-methoxythionaphthene had proceeded in the thiophene part, was proved by Raney nickel desulphurization of VI and oxidation of the resulting sulphur-free product giving *p*-anisic acid. The non-identity of VII with authentic γ-(6-methoxy-3-thionaphthenyl)-butyric acid (VIIIc described later), further showed that the succinoyl group was oriented in the 2-position as shown in VI.

The next approach to IV, was through cyclization of IXa although during the synthesis of V, unsuccessful attempts were made to cyclize IXb it was hoped that due to the strong mesomeric effect of the *para*-methoxy group, cyclization of IXa might succeed. Halogenation of *m*-methoxythiophenol led to a chlorinated derivative of

[8] A. V. Sunthanker and B. D. Tilak, *Proc. Indian Acad. Sci.* **33A**, 35 (1951).
[9] C. Hanzch and B. Schmidhalter *J. Org. Chem.* **20**, 1056 (1955).
[10] L. F. Fieser and R. G. Kennelly, *J. Amer. Chem. Soc.* **57**, 1611 (1935).
[11] P. Hill, W. F. Short and A. Higginbottom, *J. Chem. Soc.* 319 (1936).

m-methoxy-benzenesulphenyl chloride. Interaction of the latter and the sodio derivative of cyclohexane-1,3-dione gave a very small yield of an impure product which analysed for $C_{13}H_{12}O_3SCl_2$ and may be represented by IXc. Attempts to

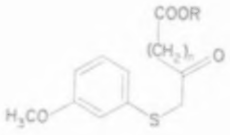


prepare the sulphenyl bromide gave similar results.

VIIIa; n = 3, X = C_2H_5 IXa; R = OCH_3, $R_1 = R_2 = H$
VIIIb; n = 2, X = H IXb; R, R_1, R_2 = H
VIIIc; n = 3, X = H IXc; R = OCH_3, $R_1 = R_2 = Cl$

Finally IV was synthesized as follows: Condensation of *m*-methoxythiophenol with ethyl 6-chloro-5-oxo-caproate (Xa) in pyridine gave ethyl 6-(*m*-methoxyphenyl-mercapto)-5-oxo-caproate (XIa). Cyclization of the latter with polyphosphoric acid gave ethyl γ-(6-methoxy-3-thionaphthenyl)-butyrate (VIIIa) which after saponification to VIIIc may by cyclized to IV.

The chloroketoester Xa was prepared by reacting γ-carboethoxybutyrl chloride[12] with diazomethane to give XIIa and passing hydrogen chloride through the ethereal solution of the diazoketone. The diazoketone synthesis and subsequent treatment with halogen acid[13] and condensation with the mercaptan[14] were carried out according to well-established procedures. Compound Xa is unstable and failed to give accurate analyses. Raney nickel desulphurization of VIIIc and oxidation of the product gave *p*-anisic acid, furnishing proof that the side chain in XIa had cyclized in the *para*-position to the methoxy group. The non-identity of VIIIc and VII obtained earlier showed that succinoylation in 6-methoxythionaphthene had occurred in the 2-position.



X—XCH_2—CO—$(CH_2)_n$—COOR
Xa; X = Cl, n = 3, R = C_2H_5
Xb; X = Cl, n = 2, R = CH_3

XIa; n = 3, R = C_2H_5
XIb; n = 2, R = CH_3

XII—N_2CH—CO—$(CH_2)_n$—COOR
XIIa; n = 3, R = C_2H_5
XIIb; n = 2, R = CH_3

Since glutaric acid required for the synthesis of XIIa is difficultly accessible and expensive, attempts were made to employ succinic acid instead extending the side

[12] W. E. Bachmann, S. Kushner and A. C. Stevenson, *J. Amer. Chem. Soc.* **64**, 974 (1942).
[13] J. Walker, *J. Chem. Soc.* 1304 (1940).
[14] J. E. Banfield, W. Davies, N. W. Gamble and S. Middleton, *J. Chem. Soc.* 4795 (1956).

chain by an Arndt–Eistert homologation. Thus β-carbomethoxy-propionyl chloride[15] was treated with diazomethane to give XIIb, which with hydrogen chloride gave Xb. Condensation of Xb with *m*-methoxythiophenol gave XIb, which was cyclized and the product saponified to give β-(6-methoxy-3-thionaphthenyl)-propionic acid (VIIIb). The yield in the Arndt–Eistert homologation of VIIIb to VIIIc was, however, poor (about 10%) and this route to VIIIc was, therefore, rejected.

Before applying Johnson's equilenin synthesis[16] (successfully employed earlier for the synthesis of the 3-desoxythioster (I) of equilenin[2,3] the Stobbe condensation of IV with diethyl succinate was studied and the desired β-carbethoxy-β-(1,2-dihydro-7-

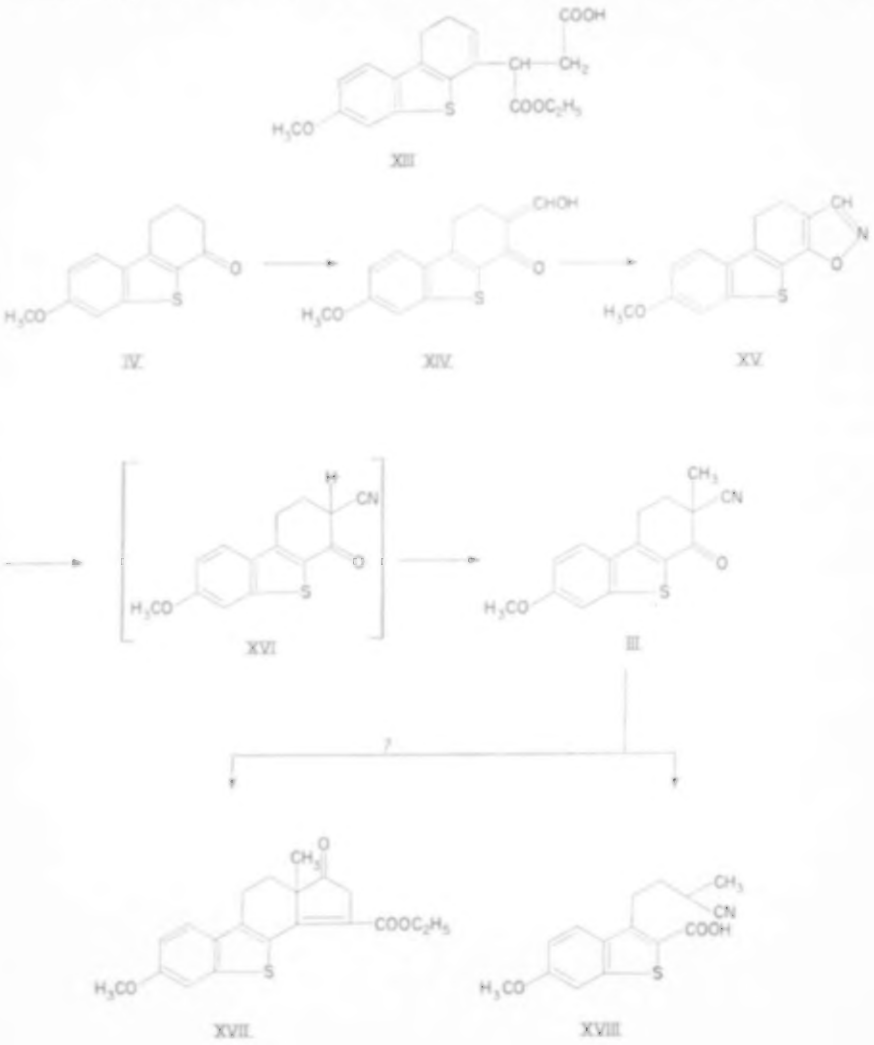


Chart I.

[15] J. Cason, *Organic Synthesis* Col. Vol. III, p. 169. John Wiley, New York (1955).
[16] W. S. Johnson, J. W. Petersen and C. D. Gutsche, *J. Amer. Chem. Soc.* **69**, 2942 (1947).

methoxydibenzothiophene-4-yl)-propionic acid (XIII) obtained, though in poor yield (24%).

Compound IV was then converted to 3-cyano-7-methoxy-3-methyl-4-oxo-1,2,3,4-tetrahydrodibenzothiophene (III) as shown in the Chart I. It is not necessary to isolate 3-cyano-7-methoxy-4-oxo-1,2,3,4-tetrahydrodibenzothiophene (XVI) formed during the conversion of XV to III, although the product was isolated for characterization.

All attempts at conversion of III to XVII by Stobbe condensation with diethyl or dimethyl succinate under a variety of conditions were unsuccessful. Under the mild conditions as in the desoxy series,[2,3] the methyl-ketonitrile was recovered unchanged, whereas under more drastic conditions (eg. condensation at 70°), the alicyclic ring was cleaved with the formation of 3-(3'-cyanobutyl)-2-carboxy-6-methoxy-thionaphthene (XVIII). A similar ring-scission has been noticed by Johnson[16]. The synthesis of the equilenin thioster (Ia) though III has, therefore, to be abandoned and the synthesis from IV by the Bachmann route[17] is under way.

EXPERIMENTAL

6-Methoxythionaphthene. A modification of the method followed earlier[8] results in improved yields.

A solution of *ω*-dimethoxyethyl *m*-methoxyphenyl sulphide[8] (1 g) in dry chlorobenzene (15 ml) was added to a mixture of phosphorus pentoxide (3 g) and syrupy phosphoric acid (11·5 g), and the mixture heated under reflux for 3½ hr. On cooling the chlorobenzene layer was decanted and the residue extracted thrice with 10 ml of benzene, and the latter washed with 2% aqueous sodium hydroxide, then with water and dried. After removal of the solvent the 6-methoxythionaphthene (0·61 g; 85% yield) was distilled b.p. 145–155° (bath) at 15 mm. The crude product gave a *picrate*, m.p. 102–103° (reported[8] m.p. 105–106°).

In runs with larger amounts of the sulphides, the yields were slightly lower (75–80%).

Demethylation of 6-methoxythianaphthene. Demethylation of crude 6-methoxythionaphthene (0·6 g), with pyridine hydrochloride (4 g) was carried out according to the method used earlier.[8] The crude hydroxythionaphthene was obtained as a brown oil (0·3 g; 55% yield). Distillation gave a pale yellow oil (0·26 g), b.p. 180–185° (bath)/13 mm which crystallized into long needles, 100–102°. Purification from a mixture of benzene and pet ether gave *6-hydroxythionaphthene* as colourless needles, m.p. 102–103° (lit[8] 102–102·5°). (Found: C, 63·8; H, 4·4; C_8H_6OS requires: C, 64·0; H, 4·0%). No 4-hydroxythionaphthene could be traced in the above reaction.

Methyl β-(6-methoxy-2-thionaphthenoyl)-propionate (VI). A solution of freshly distilled anhydrous stannic chloride (1·7 ml) in dry thiophene-free benzene (10 ml) was gradually added at 0–5° during 40 min to a stirred mixture of 6-methoxythionaphthene (1·85 g), *β*-carbomethoxypropionyl chloride[15] (1·7 g), and dry thiophene-free benzene (10 ml). The temp maintained at 0–5° for another 30 min and then allowed to 30° during 1 hr. The reaction mixture was stirred further for 1½ hr at room temp and then poured into a mixture of crushed ice and dil HCl. The orange-coloured benzene layer (washed with 2% aqueous NaOH, and water) left a residue which on crystallization from ether gave VI as small needles (1·12 g; 36% yield), m.p. 92–95°. Two recrystallizations from isopropyl ether gave VI as fine colourless needles, m.p. 96–97·5°. (Found: C, 60·5; H, 5·2; S, 11·2. $C_{14}H_{14}O_4S$ requires: C, 60·4; H, 5·0; S, 11·5%).

Raney nickel desulphurization of VI *and oxidation of the desulphurized product.* A mixture of VI (0·2 g), Raney nickel (2·5 g) and ethanol (30 ml) was refluxed under stirring for 6½ hr. After removal of nickel by filtration, alcohol was removed and the oily residue (negative sulphur test) heated with 5% aqueous HNO_3 (10 ml) in a sealed tube at 150–180° for 12 hr. On cooling, *p*-anisic acid, m.p. 185°, separated.

γ-(6-Methoxy-2-thionaphthenyl)-butyric acid (VII). A mixture of mossy zinc (1 g), mercuric chloride (0·1 g), conc HCl (0·1 ml), and water (1·5 ml) was shaken for 5 min; the supernatant

[17] W. E. Bachmann, Wayne Cole and D. C. Wilds, *J. Amer. Chem. Soc.* **62**, 814 (1940).

solution decanted off, and the other reagents were added in the following order: Water (1 ml), conc HCl (1·75 ml), toluene (1·5 ml) and VI (0·5 g). The mixture was refluxed briskly for 36 hr, HCl (3 ml) portions being added at 6 hr intervals. The product, a dark yellow oil, was saponified by refluxing with baryta (0·5 g) in 80% aqueous ethanol (20 ml) for 1½ hr. After removal of ethanol under reduced pressure, the residue was acidified with HCl and ether-extracted. The ether solution was shaken with aqueous sodium bicarbonate solution. Acidification of the alkaline extract gave VII as a dark resinous solid. On distillation the latter gave a white crystalline solid (0·155 g), b.p. 150–160°/0·07 mm (yield, 35%) which crystallized from aqueous methanol in white flakes, m.p. 77°. (Found: C, 62·3; H, 5·3; S, 13·2. $C_{13}H_{14}O_3S$ requires: C, 62·4; H, 5·6; S, 12·8%).

2-(m-*Methoxy-dichlorophenylmercapto*)-*cyclohexane*-1,3-*dione* (IXc). The calculated amount of dry chlorine was slowly bubbled through a stirred solution of *m*-methoxythiophenol (2 g) in chloroform (30 ml) at 0° for 1 hr. After 30 min the solvent was removed and the residual oil dissolved in dry benzene (25 ml) and a mixture of cyclohexane-1,3-dione (1·6 g) and sodium methoxide (prepared from 0·33 g of sodium) added. The mixture was refluxed for 4 hr, filtered, solvents distilled off and the dark oily residue triturated with ether. After leaving in the refrigerator for several days, yellowish-white crystals separated (0·28 g, m.p. 150–155°). Repeated crystallizations from dil ethanol afforded white needles, m.p. 157°. (Found: C, 50·3; H, 3·9; Cl, 23·1. $C_{13}H_{12}O_3Cl_2S$ requires: C, 48·9; H, 3·8; Cl, 22·3%).

Repeated crystallizations failed to give a purer product.

Ethyl 6-*chloro*-5-*oxocaproate* (Xa). A solution of γ-carbethoxybutyryl chloride[12] (10·9 g) in dry ether (20 ml) was added slowly under vigorous agitation to an ethereal diazomethane solution prepared from nitrosomethyl urea (20 g) at 0–5°. After keeping for 2 hr in cold, most of the ether was removed under reduced pressure at 20–25°. Dry hydrogen chloride gas was then passed through the cooled ethereal solution of the diazoketone for 15 min. Removal of ether gave Xa as a yellow oil (10 g), b.p. 88–94°/0·5 mm (yield 84%). The compound being unstable was immediately condensed with *m*-methoxythiophenol.

Ethyl 6-(m-*methoxyphenylmercapto*)-5-*oxocaproate* (XIa). Compound Xa (11 g) was gradually added under cooling to a solution of *m*-methoxythiophenol (6 g) in pyridine (30 ml). After keeping overnight, the mixture was diluted with 1:1 aqueous HCl and extracted with ether. The ether extract gave an oil which on fractional distillation gave a pale-yellow viscous oil (7·4 g, yield 60%), b.p. 155–160°/0·0025 mm. (Found: C, 60·3; H, 6·3; S, 11·3. $C_{15}H_{20}O_4S$ requires: C, 60·8; H, 6·8; S, 10·8%).

Ethyl γ-(6-*methoxy*-3-*thionaphthenyl*)-*butyrate* (VIIIa). To polyphosphoric acid, obtained from phosphorous pentoxide (12 g) and phosphoric acid (6 ml), was added a solution of XIa (4 g) in benzene (50 ml). The mixture was heated under reflux for 3 hr. The benzene layer was decanted off and the tarry residue extracted twice with boiling benzene. Removal of benzene and distillation gave VIIIa as a pale-yellow oil (3·2 g; yield 83%), b.p. 135–140° (bath)/0·007 mm. (Found: C, 64·4; H, 6·5; S, 11·8. $C_{15}H_{18}O_3S$ requires: C, 64·8; H, 6·5; S, 11·5%).

γ-(6-*Methoxy*-3-*thionaphthenyl*)-*butyric acid* (VIIIc). Compound VIIIa (1·3 g) was hydrolysed by refluxing with baryta (2 g) in 80% ethanol (25 ml) for 1½ hr. After removal of ethanol under reduced pressure, the residue was acidified with HCl and the mixture left overnight. The white crystalline solid which separated was filtered, washed and dried (1·2 g; yield quantitative). Repeated crystallizations from benzene afforded VIIIc as white needles, m.p. 160°. (Found: C, 62·7; H, 5·7; S, 13·2. $C_{13}H_{14}O_3S$ requires: C, 62·4; H, 5·6; S, 12·8%).

Raney nickel desulphurization of VIIIc and oxidation of the desulphurized product (as described earlier for the degradation of compound VI) gave *p*-anisic acid.

7-*Methoxy*-4-*oxo*-1,2,3,4-*tetrahydrodibenzothiophene* (IV). A solution of once-crystallized VIIIc (1 g) m.p. 154–156° in glacial acetic acid (10 ml) and acetic anhydride (20 ml) was treated with a freshly prepared 2% solution of fused zinc chloride in acetic acid (10 ml). The mixture was heated under reflux in a nitrogen atmosphere for 4 hr. The solution cooled and diluted with water yielded VI (0·9 g, yield 96%) which crystallized from ethanol, as white flakes, m.p. 155°. (Found: C, 67·2; H, 4·8; S, 14·3. $C_{13}H_{12}O_2S$ requires: C, 67·2; H, 5·2; S, 13·8%).

The 2,4-*dinitrophenylhydrazone* crystallized from chloroform in bright red plates, m.p. 278°. (Found: N, 13·5. $C_{19}H_{16}O_6N_4S$ requires: N, 13·6%).

Methyl 5-*chloro*-4-*oxo*-*valerate* (Xb). β-Carbomethoxypropionyl chloride[13] (16 g) was converted to methyl 5-chloro-4-oxo-valerate (Xb) as for the preparation of compound Xa. The compound

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Xb, (16·4 g yield 93%), b.p. 90–95° (bath)/2 mm being unstable was used immediately without further purification. (Found: C, 44·2; H, 5·5; Cl, 18·8. $C_9H_9O_3Cl$ requires: C, 43·8; H, 5·5; Cl, 21·6%).

Methyl 5-(m-*methoxyphenylmercapto*)-4-*oxovalerate* (XIb). To a solution of *m*-methoxythiophenol (12·5 g) in pyridine (30 ml) was slowly added Xb (16 g) under cooling. The mixture was stirred vigorously for 10 min, then heated on waterbath for 15 min. The product XIb distilled as a yellow oil (9·5 g, yield 40%), b.p. 140–145° (bath/0·027 mm). (Found: C, 58·1; H, 5·8; S, 12·3. $C_{13}H_{16}O_4S$ requires: C, 58·2; H, 6·0; S, 11·9%).

β-(6-*Methoxy*-3-*thionaphthenyl*)-*propionic acid* (VIIIb). Compound XIb, (9·5 g) was cyclized by treatment with a mixture of phosphorous pentoxide (30 g), phosphoric acid (15 ml) and chlorobenzene (100 ml) at boiling point for 3 hr. The cyclization product was then saponified by refluxing with baryta (9 g) in 80% aqueous ethanol (100 ml) for 1½ hr. The acid (VIIIb) was isolated by extraction with ether and purified by dissolution in aqueous sodium bicarbonate. The acid (4·5 g, yield 54% from XIb) crystallized from ethanol in white needles, m.p. 141°. (Found: C, 60·8; H, 5·6; S, 14·0. $C_{12}H_{12}O_3S$ requires: C, 61·0; H, 5·1; S, 13·6%).

Homologation of (VIIIb) *to γ*-(6-*methoxy*-3-*thionaphthenyl*)-*butyric acid* (VIIIc). The acid VIIIb (1 g) was converted to the acid chloride with thionyl chloride (1·5 ml) in dry benzene (5 ml) at room temp for 30 min and then heating under reflux at 40° for 15 min. After removal of solvent and thionyl chloride, the acid chloride was re-dissolved in dry benzene (20 ml) and the solution slowly added under vigorous agitation and ice-cooling (0–5°) to an ethereal diazomethane solution prepared from nitrosomethyl urea (3 g). The diazoketone obtained was dissolved in dioxan (10 ml) and the solution added dropwise with stirring to a mixture of silver oxide (0·2 g), anhydrous sodium carbonate (0·5 g), sodium thiosulphate (0·3 g), and water (20 ml) at 50–60°. Stirring was continued for 1 hr and the temp raised to 90–100°. The solution was cooled, diluted with water, acidified with dil HNO_3 and extracted with ether. The acid VIIIc (0·12 g) was isolated from the ether extract by means of sodium bicarbonate. Crystallization of the crude acid from benzene afforded white needles, m.p. 160°, undepressed on admixture with VIIIc prepared earlier starting from glutaric acid.

β-*Carbethoxy*-*β*-(1,2-*dihydro*-7-*methoxydibenzothiophen*-4-*yl*)-*propionic acid* (XIII). To a cooled solution of potassium (0·13 g) in dry t-butanol (10 ml) was added diethyl succinate (1·3 ml) followed by the ketone IV (0·5 g). After evacuation of air the mixture was covered with nitrogen and shaken mechanically at room temp (27–29°) for 4 hr during which a faint yellowish-orange colouration developed. The mixture was then heated for 5 min on a water bath at 40–45° with shaking. Acidification of the cooled reaction mixture gave a brown coloured oil. Butanol was removed under reduced pressure and the semi-solid residue taken up in ether and extracted with aqueous sodium bicarbonate. The ether extract contained unchanged starting ketone IV (0·21 g). The bicarbonate extract, on acidification, gave yellowish-white flakes of XIII (0·19 g, yield 24%), m.p. 84–86°. Three recrystallizations from ethanol gave nearly colourless needles, m.p. 87–87·5°. (Found: C, 61·5; H, 6·0; S, 9·0. $C_{19}H_{20}O_5S$ requires: C, 63·3; H, 5·6; S, 8·9%. Eq. wt. Found: 353; Calc. 360). For want of material, the product could not be purified further.

3-*Hydroxymethylene*-7-*methoxy*-4-*oxo*-1,2,3,4-*tetrahydrodibenzothiophene* (XIV). A solution of ethyl formate (2 ml) in dry thiophene-free benzene (10 ml) was added to freshly prepared sodium methoxide [from sodium (0·5 g) and absolute methanol (10 ml), evaporation of methanol and drying the methoxide under reduced pressure at 200°]. After evacuation of air, the flask containing the mixture was filled with nitrogen. The mixture was cooled and a solution of the ketone IV (1 g) in dry benzene (30 ml) was added. The flask was again filled with nitrogen as above, stoppered, and shaken mechanically for 5 hr at room temp. The mixture was treated with water, and the benzene layer washed with water and then with aqueous sodium hydroxide. The combined aqueous portions, on acidification, gave the hydroxymethylene derivative (XIV) as a pale yellow solid (1·11 g; yield 99%). Repeated crystallizations from ethanol gave pale yellow needles, m.p. 128°. (Found: C, 64·6; H, 4·8; S, 12·5. $C_{14}H_{12}O_3S$ requires: C, 64·6; H, 4·6; S, 12·3%).

7-*Methoxy*-9,10-*dihydrodibenzothiopheno*-(3,4-d)-*isoxazole* (XV). A mixture of the crude hydroxymethylene ketone (XIV) (1·11 g, m.p. 112–115°), hydroxylamine hydrochloride (0·7 g) and glacial acetic acid (25 ml) was refluxed at 160–170° (oil bath). After heating for 20 min boiling water (25 ml) was added to the hot mixture causing crystallization. After 2 hr in the refrigerator, the crystalline product was filtered, washed and dried. The product was dissolved in ether–benzene and the solution washed twice with 2% aqueous NaOH and then with water. Removal of solvents gave a

brownish-white crystalline residue (0·78 g; yield 70%, m.p. 147–149°). Crystallization from benzene gave the isoxazole (XV) as light brown plates, m.p. 150°. (Found: C, 65·2; H, 4·2; N, 5·2. $C_{14}H_{11}O_2NS$ requires: C, 65·4; H, 4·3; N, 5·5%).

3-*Cyano*-7-*methoxy*-4-*oxo*-1,2,3,4-*tetrahydrodibenzothiophene* (XVI). The crude isoxazole XV (0·28 g, m.p. 138–140°) was added to a solution of potassium (0·17 g) in t-butanol (6 ml). The yellow potassium derivative of the β-ketonitrile separated out. The mixture was heated under reflux for 1 hr, cooled and diluted with water. The mixture was extracted with ether and the aqueous solution set aside. The ethereal layer was washed once with 10% aqueous NaOH. The combined alkaline extracts on careful acidification in cold gave dark-brown needles of the cyanoketone (XVI, 0·16 g, m.p. 173–175°). Several recrystallizations from ethanol gave fine light brown needles, m.p. 180°. (Found: C, 65·6; H, 4·4; N, 5·2. $C_{14}H_{11}O_2NS$ requires: C, 65·4; H, 4·3; N, 5·5%).

3-*Cyano*-7-*methoxy*-3-*methyl*-4-*oxo*-1,2,3,4-*tetrahydrodibenzothiophene* (III). Potassium (0·4 g) was dissolved in dry t-butanol (15 ml) and XV (0·86 g) was added with separation of a yellow precipitate. The mixture was refluxed with stirring for 1½ hr (water bath temp 90–100°) and the bath temp then reduced to 75–80°, and methyl iodide (5 ml) added dropwise during 30 min. Heating under reflux with stirring was continued for 2 hr. After removal of butanol (reduced pressure) the pale yellow residue was extracted with ether–benzene and the extract washed (water and 10% aqueous NaOH). The product from ethanol gave nearly colourless plates of the methyl cyanoketone III (0·7 g, yield 78%), m.p. 154° after further crystallizations. (Found: C, 66·5; H, 4·6; N, 5·3; S, 11·8; OMe, 11·4. $C_{15}H_{13}O_2NS$ requires: C, 66·4; H, 4·8; N, 5·2; S, 11·8; OMe, 11·4%).

Stobbe reaction on (III)

A. *Mild conditions*. To a cooled solution of potassium (0·12 g) in t-butanol (10 ml), diethyl succinate (1·5 ml) was added followed by the ketonitrile (III, 0·2 g). After evacuating air, the flask was filled with nitrogen, stoppered and shaken mechanically for 6 hr at room temp. The reaction mixture was acidified with dil HCl, butanol removed (reduced pressure) leaving a yellowish residue from which the unchanged ketone (III, 0·13 g, m.p. 153–154°) was recovered.

Similar results were obtained when dimethyl succinate, potassium methoxide, sodium hydride, sodium methoxide, sodium t-butoxide, etc. were employed and the reaction carried out at room temperature.

B. *Vigorous conditions*. To a solution of potassium (0·15 g) dissolved in dry t-butanol (10 ml), was added under nitrogen atmosphere diethyl succinate (1·2 ml), followed by a warm solution of III (0·26 g) in t-butanol (25 ml). The colour of the reaction mixture changed immediately to lemon yellow. After shaking mechanically for 5 hr under nitrogen atmosphere, the colour deepened to reddish-brown. The flask was then heated on a water-bath at 70° for 30 min and the product worked up as usual. The alkali washings on acidification yielded a pale yellow solid which was purified by extraction of its ethereal solution with aqueous sodium bicarbonate. The bicarbonate solution on acidification afforded yellowish white crystals (0·2 g) of 3-(3′-cyanobutyl)-2-carboxy-6-methoxythionaphthene (XVIII), m.p. 162–164°, m.p. 165° after crystallization from ethanol (Found: C, 62·3; H, 5·2; S, 11·3. $C_{15}H_{15}O_3NS$ requires: C, 62·3; H, 5·2; S, 11·1%).

Other experiments carried out at the boil using dimethyl succinate, sodium hydride, sodium t-butoxide, etc. and employing a large volume of t-butanol to dissolve the sparingly soluble ketone (III) also gave XVIII as the major product.

Acknowledgements—The authors wish to thank the Council of Scientific and Industrial Research, Government of India, for research grants and Dr. T. S. Gore for the microanalyses recorded in this paper.

Tetrahedron, 1960, Vol. 10, pp. 223 to 229. Pergamon Press Ltd. Printed in Northern Ireland

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SYNTHESIS OF HETEROCYCLIC STEROIDS—IV*

SYNTHESIS OF DL-B-NOR-6-OXAEQUILENIN

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(*Received* 31 *March* 1960)

Abstract—The synthesis of dl-B-nor-6-oxaequilenin starting from 7-methoxy-4-oxo-1,2,3,4-tetrahydrodibenzofuran is described. The latter compound was prepared from the known γ-(2,4-diydroxybenzoyl)-butyric acid.

THE synthesis of dl-B-nor-6-oxaequilenin (I), the furano analogue of equilenin (II), was undertaken as a part of the work on the total synthesis of heterocyclic steroids.[1] Among the oxygen-containing steroids reported, are certain coumarino-steroids some of which are derived naturally by degradation and resynthesis.[2]

dl-B-nor-6-oxaequilenin (I) was synthesized starting from resorcinol, following the Johnson *et al.*[3] equilenin synthesis. Part of this work has been reported earlier[4] and the present paper gives details and further work.

7-Methoxy-4-oxo-1,2,3,4-tetrahydrodibenzofuran (III) was prepared in a 24 per cent yield from γ-(2,4-dihydroxybenzoyl)-butyric acid[5] (IV), and in 10 per cent yield from *m*-methoxyphenol as shown in Chart 1.

Once the cyclopenteno-D-ring was built up, as in XVI the compound exhibited pronounced instability to air both in alkaline medium and neutral solutions. All subsequent reactions were, therefore, carried out in an atmosphere of nitrogen.

The 14,15-dehydro-structure was assigned to XVII by analogy with Johnson's equilenin synthesis[3] and also on the basis of spectral evidence. Johnson isolated two dehydro compounds,[3] and 14,15- and 15,16-dehydro structures XX and XXI were assigned to the higher and the lower melting compounds respectively on the basis of spectral evidence.

In the present work only one isomer (XVII) was isolated on elimination of the carbethoxy group from XVI. The product XVII is represented as the 14,15-dehydro isomer wherein the cyclopenteno double bond is in conjugation with the benzofuran chromophore and is not as the isomeric α:β-unsaturated ketone (XVIII). This was proved by a comparison of U.V. spectra of the decarboxylated product and those of 7-methoxy-1,2,3,4-tetrahydrodibenzofuran (XXII) and B-nor-6-oxaequilenin methyl ether (XIX), Fig. 1. The spectra of XXII and XIX are nearly identical, whereas in the decarboxylated product XVII the 7-methoxy-1,2,3,4-tetrahydrodibenzofurano

* Part III: *Tetrahedron* **10**, 215 (1960)

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[2] Ng. Ph. Buu-Hoï and D. Lavit, *J. Org. Chem.* **21**, 1022 (1956); W. W. Westerfeld, *J. Biol. Chem.* **143**, 177 (1942); R. P. Jacobsen, H. Levy and R. Daniels, *J. Biol. Chem.* **171**, 61, 71, 81 (1947); L. M. Thompson, C. H. Yates and A. D. Odell, *J. Amer. Chem. Soc.* **76**, 1194 (1954).
[3] W. S. Johnson, J. W. Petersen and C. D. Gutsche, *J. Amer. Chem. Soc.* **69**, 2942 (1947).
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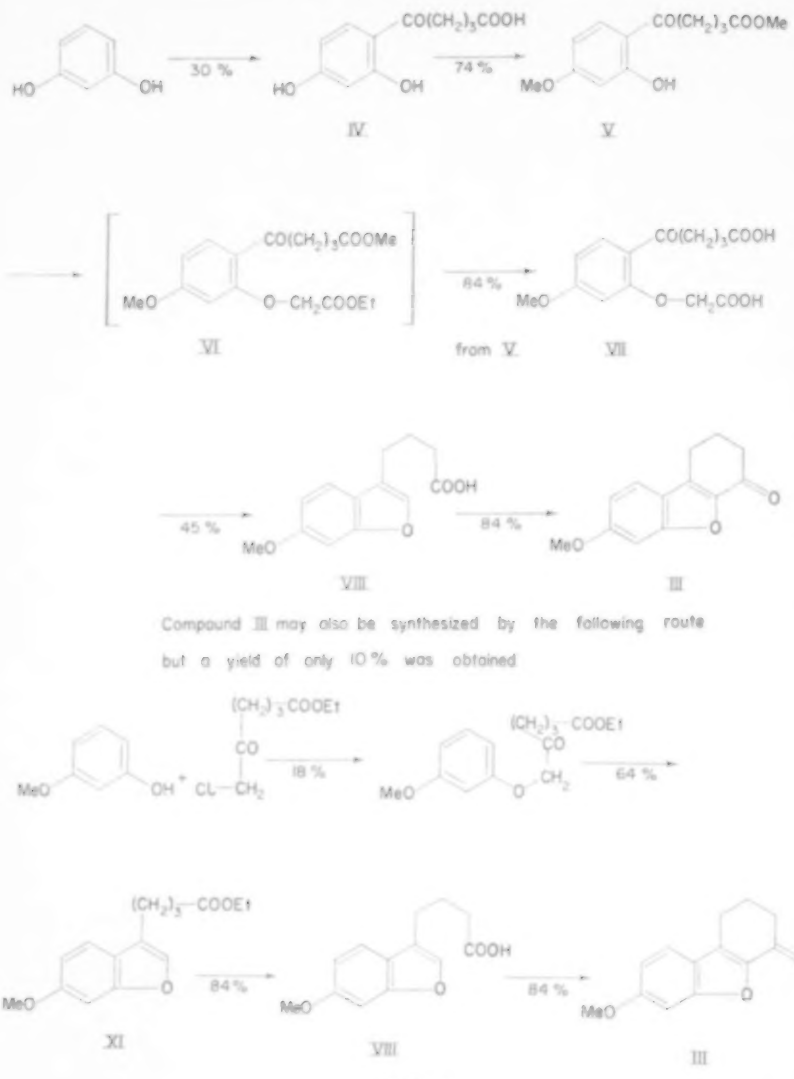

Compound III may also be synthesized by the following route but a yield of only 10% was obtained

Chart I

chromophore is no longer distinguishable. The increased intensity at higher wavelengths (300 mμ to 320 mμ) indicates that the cyclopenteno double bond in XVII is in conjugation with the benzofurano chromophore as shown in the structure for XVII. If the latter compound has the alternative structure XVIII, its spectrum would be similar to that of XXII and XIX since the principal maxima due to the $\alpha:\beta$-unsaturated ketonic function in XVIII would be expected to lie in the unexamined region of shorter wavelengths.[3,6] Although XVIII was not isolated, its presence in the mother liquors left after separation of XVII cannot be ruled out.

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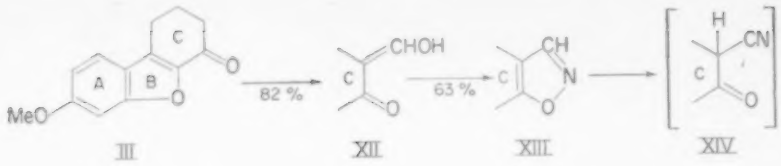
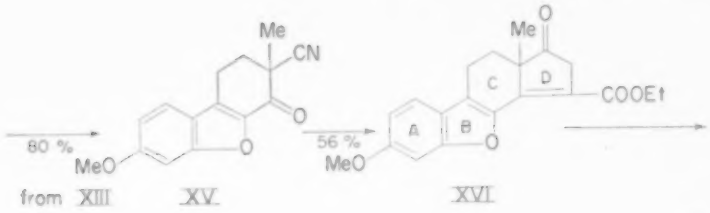
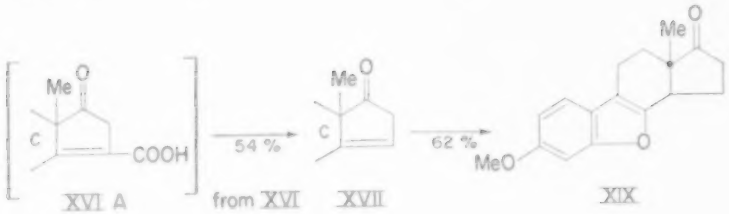


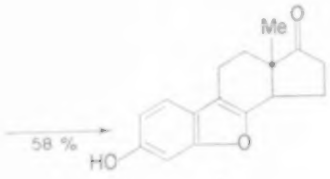
III XII XIII XIV



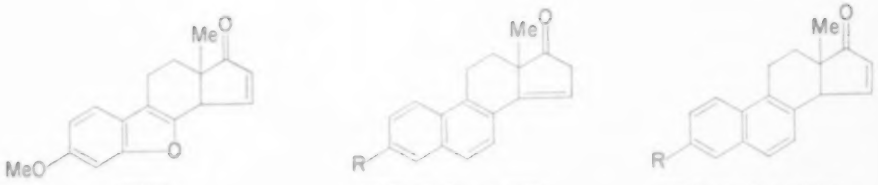
from XIII XV XVI



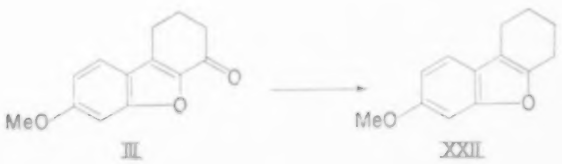
XVI A from XVI XVII XIX



I



XVIII XX, R = H or OMe XXI, R = H or OMe



III XXII

Chart II

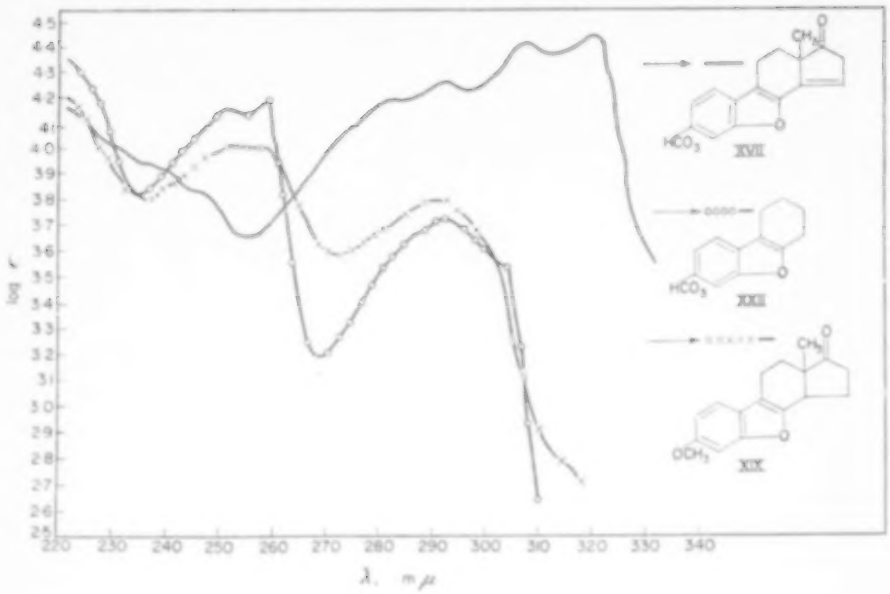


FIG. 1.

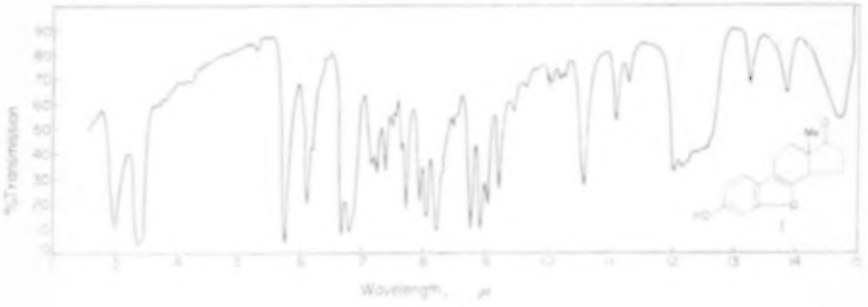


FIG. 2.

7-Methoxy-1,2,3,4-tetrahydrodibenzofuran (XXII) was prepared from the ketone (III) by Clemmensen reduction for the purpose of spectral examination.

In B-nor-6-oxaequilenin methyl ether (XIX) the C/D rings are *trans*-fused and the angular C-18-methyl group is represented by the β-configuration. This structure is suggested by analogy with Johnson's observation that catalytic hydrogenation of 14,15-dehydroequilenin methyl ether (XX, R = OCH_3) under neutral conditions leads predominantly to C/D *trans*-fusion. It is, however, necessary to provide unambiguous proof since stereochemical analogy between natural steroids and their heterocyclic analogues has not been experimentally established. The ultra-violet absorption spectra of XIX and XXII are similar and showed a maximum at 292 mμ characteristic of the benzofuran chromophore. Demethylation of the XIX gives dl-B-nor-6-oxaequilenin (I). The infra-red spectrum (Nujol mull) shows the bands at 3,311 cm^{-1} (3·02 μ) and 1730 cm^{-1} (5·78 μ) indicating the presence of the 3-hydroxy group and the cyclopentano-keto group, respectively (Fig. 2). The ultra-violet absorption spectra of I

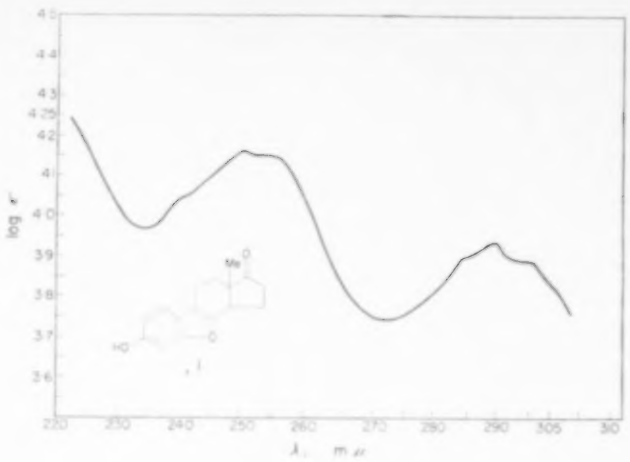


FIG. 3.

and XIX are similar and they show a maximum at 292 mμ characteristic of the benzofuran chromophore (Figs. 1 and 3).

The overall yield of I from the ketone III was 3·5%. The estrogenic and carcinogenic activity of dl-B-nor-6-oxa-equilenin (I), will be examined. The optical resolution of the compound could not be undertaken due to lack of the material.

EXPERIMENTAL

Methyl γ-(2-hydroxy-4-methoxybenzoyl)-butyrate (V). To a solution of γ-(2,4-dihydroxybenzoyl)-butyric acid[5] (IV, 3·6 g) and dimethyl sulphate (3 cc) in dry acetone (50 cc), anhydrous potassium carbonate (15–18 g) was added. The mixture was refluxed for 6 hr, acetone distilled off and the residue diluted with water and crystallized from n-hexane as white needles, m.p. 58°, yield 3 g. (Found: C, 61·5; H, 6.5. $C_{13}H_{16}O_5$ requires: C, 61·9; H, 6·4%).

γ-(2-Carboxymethoxy-4-methoxybenzoyl)-butyric acid (VII). The ester V (5·04 g) was dissolved in dry ethyl methyl ketone (100 cc) and ethyl bromacetate (2·8 cc) and anhydrous potassium carbonate (11·6 g) added. The mixture was refluxed for 7 hr, ethyl methyl ketone removed and water added. The intermediate product (VI) was hydrolysed by boiling with 10% aqueous sodium hydroxide (45 cc) and ethanol (35 cc) under reflux for 2 hr. Ethanol was distilled off and the residual solution acidified. The precipitated acid, on crystallization from water gave VII as white needles, m.p. 155°, yield 5·1 g. (Found: C, 56·8; H, 5·1. $C_{14}H_{16}O_7$ requires: C, 56·7; H, 5·4%).

3-ω-Carboxypropyl-6-methoxybenzofuran (VIII). A mixture of VII (3·8 g), fused sodium acetate (12 g) and acetic anhydride (40 cc) was heated under reflux for 5 hr, at 160–70° (oil bath) with evolution of carbon dioxide. The reaction mixture was diluted with hot water and kept overnight. The product was filtered washed acid-free and extracted with sodium bicarbonate solution, leaving an insoluble portion which crystallized from ethanol in needles, m.p. 129°, identical with III. Acidification of the sodium bicarbonate extract gave VIII which crystallized from water in white needles, m.p. 106°, yield 1·2 g. (Found: C, 66·6; H, 5·9. $C_{13}H_{14}O_4$ requires: C, 66·6; H, 6·0%)

7-Methoxy-4-oxo-1,2,3,4-tetrahydrodibenzofuran (III). A mixture of VIII (7·1 g), acetic anhydride (125 cc) and glacial acetic acid (65 cc) was added to a solution of zinc chloride in acetic acid (20%, 65 cc). The mixture was refluxed for 4 hr at 160–70° (oil bath) under nitrogen atmosphere. Acetic acid and acetic anhydride were removed (reduced press) and the residue was filtered washed and then treated with sodium bicarbonate solution to remove unchanged VIII. Crystallization of the product from ethanol, gave III as pale orange needles, m.p. 129°, yield 5·4 g. (Found: C, 77·2; H, 5·6. $C_{13}H_{12}O_3$ requires: C, 77·2; H, 5·6%). The *semicarbazone* crystallized in shining white silky needles, m.p. 235° (decomp). (Found: C, 61·9; H, 5·3; N, 15·3. $C_{14}H_{15}O_3N_3$ requires: C, 61·5; H, 5·5; N, 15·3%).

Ethyl 6-(m-*methoxyphenoxy*)-5-*oxo-caproate* (X). Resorcinol mono-methyl ether (1·24 g) was refluxed for 3 hr with anhydrous potassium carbonate (4·5 g) in presence of ethyl methyl ketone (25 cc). To this ethyl 6-chloro-5-oxo-caproate IX (2·3 g) was added and the mixture refluxed for 4 hr, the solvent removed, water added and the mixture extracted with ether and the extract washed with 10% aqueous sodium hydroxide and water. The product was distilled, unreacted IX was removed at 100–120°/1·2 mm and X was collected at 155–160°/0·01 mm as a colourless liquid, yield 0·2 g. (Found: C, 64·6; H, 7·0. $C_{15}H_{20}O_5$ requires: C, 64·2; H, 7·2%).

3-*ω-Carbethoxypropyl-methoxybenzofuran* (XI). A solution of X (0·2 g) in dry benzene (20 cc) was added to polyphosphoric acid (mixture of 0·6 g of P_2O_5 and 0·6 g of H_3PO_4) and the deep blue coloured mixture refluxed for 3 hr. The benzene layer was decanted and the residue extracted twice with 15 cc portions of benzene. The polyphosphoric acid residue was diluted with ice water and the mixture extracted with ether and benzene. The total ether–benzene extracts were washed with aqueous sodium bicarbonate and water. Removal of the solvents gave XI which distilled at 120–125°/0·01 mm, as a pale yellow viscous liquid, yield 0·125 g. (Found: C, 69·0; H, 6·9. $C_{15}H_{18}O_4$ requires: C, 68·7; H, 6·9%).

3-*ω-Carboxypropyl-6-methoxybenzofuran* (VIII). Finely powdered barium hydroxide octahydrate (0·085 g) was added to a solution of XI (0·08 g) in 80% aqueous ethanol (10 cc) and the mixture refluxed for 3 hr. After removal of ethanol the mixture was diluted with water and acidified with HCl and the ether extract treated with aqueous sodium bicarbonate. Acidification gave VIII m.p. 106°. A mixed m.p. with the authentic specimen (prepared earlier) was not depressed.

3-*Hydroxymethylene-7-methoxy-4-oxo*-1,2,3,4-*tetrahydrodibenzofuran* (XII). A mixture of dry sodium methoxide (from 0·07 g sodium), ethyl formate (0·07 cc), the ketone III (0·216 g) and benzene (20 cc) was shaken mechanically under nitrogen atmosphere for 6 hr. The mixture was ether extracted and the product isolated with aqueous sodium hydroxide. Acidification gave XII (0·2 g) which crystallized from aqueous ethanol in pale yellow micro-crystalline flakes, m.p. 184–186°. (Found: C, 69·0; H, 5·1. $C_{14}H_{12}O_4$ requires: C, 68·8; H, 4·9%).

9,10-*Dihydro-6-methoxydibenzofurano*-(2,1-*d*)-*isoxazole* (XIII). Dry finely powdered hydroxylamine hydrochloride (0·14 g) was added to a solution of XII (0·32 g) in glacial acetic acid (7 cc) and the mixture was refluxed for 12 min at 170–175° (oil bath). After dilution with hot water (20–30 cc) and cooling the solid product was dissolved in ether and washed with aqueous sodium hydroxide (2%). The dark yellowish orange product was distilled at 190–210°/0·03–0·05 mm and the distillate crystallized from acetone (0·2 g) as pale yellow needles, m.p. 211–212°. (Found: C, 69·5; H, 4·9; N, 6·2. $C_{14}H_{11}O_3N$ requires: C, 69·7; H, 4·6; N, 5·8%).

3-*Cyano-7-methoxy-3-methyl-4-oxo*-1,2,3,4-*tetrahydrodibenzofuran* (XV). To a solution of potassium (0·78 g) in t-butanol (70 cc), XIII (1·6 g) was added and the mixture refluxed for 2 hr with separation of the yellowish green potassium salt of XIV. The solution was cooled, methyl iodide (1 cc) added and the mixture kept at room temp for 2 hr, and then refluxed gently at 120–125° (oil bath) for a further 2 hr. After cooling methyl iodide (1·5 cc) was added and the mixture refluxed for 2 hr cooled and again methyl iodide (1 cc) added and the mixture kept overnight at room temp. The next day, the mixture was refluxed for 2 hr, cooled and the last lot of methyl iodide (1·5 cc) added and refluxed vigorously for 4 hr and t-butanol removed (reduced press). The residue was extracted with ether and washed with aqueous sodium hydroxide (2%, extract A) to remove the unreacted XIV. Removal of ether gave XV (1·35 g) which crystallized from aqueous ethanol in white needles, m.p. 121°. (Found: C, 70·7; H, 5·2; N, 5·4; OMe, 13·2%. $C_{15}H_{13}O_3N$ requires: C, 70·6; H, 5·1; N, 5·5; OMe, 12·2%).

3-*Cyano-7-methoxy-4-oxo*-1,2,3,4-*tetrahydrodibenzofuran* (XIV). The alkaline extract (A) from the above experiment was acidified giving a pale greyish white solid (0·1 g), which crystallized from aqueous methanol XIV as pale yellow needles, m.p. 221–222°. (Found: C, 70·2; H, 4·6; N, 6·0. $C_{14}H_{11}O_3N$ requires: C, 69·6; H, 4·9; N, 6·2%).

15-*Carbethoxy*-14,15-*dehydro*-B-*nor-6-oxaequilenin methyl ether* (XVI). To a solution of potassium (0·341 g) in t-butanol, diethyl succinate (2·9 cc) and XV (1 g) were added. The mixture was mechanically shaken at room temp for 7 hr in nitrogen atmosphere. The reddish solution containing an orange precipitate was cooled and carefully acidified with HCl with evolution of carbon dioxide. t-Butanol was removed (reduced press) and the residue ether extracted washed with aqueous sodium hydroxide (2%) and water. The product, on crystallization from ethanol, gave XVI (0·75 g) as pale violet prisms, m.p. 135°. (Found: C, 70·9; H, 5·8. $C_{20}H_{20}O_5$ requires: C, 70·6; H, 5·9%).

14,15-*Dehydro*-B-*nor*-6-*oxaequilenin methyl ether* (XVII). To a solution of XVI (0·72 g) in ethanol (20 cc) and water (10 cc), barium hydroxide octahydrate (0·735 g) was added and the mixture refluxed for 2½ hr in nitrogen atmosphere. Ethanol was removed under a current of nitrogen and the residue decomposed by treatment with HCl. The acid was filtered, washed, dried (crude yield 0·7 g) and then dissolved in pyridine (5·6 cc). Under nitrogen atmosphere, conc HCl (11·2 cc) was added in 3 lots at 5 min intervals with evolution of carbon dioxide. The mixture was refluxed for 30 min under nitrogen at 140–150° (oil bath) and extracted with ether and the extract washed successively with dil HCl, aqueous NaOH and water. The product distilled at 165–175°/0·02–0·04 mm giving a pale yellow liquid which on solidification and keeping developed a pale violet colour. On crystallization from ethyl acetate under nitrogen, pale violet needles of XVII m.p. 161° (0·3 g) were obtained (Found: C, 75·6; H, 5·6. $C_{17}H_{16}O_3$ requires: C, 76·1; H, 5·9%). The U.V. absorption spectrum of XVII (ethanol) revealed the following principal absorption maxima: λ_{max} 292, 308, 320 mμ (log ε = 4·262, 4·423, 5·456).

B-*nor*-6-*oxaequilenin methyl ether* (XIX). Compound XVII (0·268 g) was added to a suspension of 30% palladium charcoal catalyst (0·08 g) in ethyl acetate (25 cc) previously saturated with hydrogen. Hydrogenation was carried out at room temp and atm press. The required quantity of hydrogen (for one double bond) was absorbed in 10 hr. The mixture was filtered, ethyl acetate removed and the residue distilled at 145–150°/0·015 mm yielding a colourless viscous semisolid (0·24 g). The product crystallized from benzene, as white needles m.p. 78°, yield 0·170 g. (Found: C, 75·3; H, 6·7. $C_{17}H_{18}O_3$ requires: C, 75·5; H, 6·7%). The U.V. absorption spectrum of XIX (ethanol) revealed the following principal absorption maxima: λ_{max} 252, 292 mμ (log ε = 3·784, 3·564).

dl-B-*nor*-6-*oxaequilenim* (I). The methyl ether XIX (0·27 g) was dissolved in glacial acetic acid (25 cc) and hydrobromic acid (2 cc, sp. gr. 1·4) was added and the solution refluxed for 6 hr in nitrogen atmosphere. Refluxing was continued for 21 hr after addition of HBr in 6 lots of 2 cc at intervals of 3 hr. Acetic acid was removed, (reduced press) the residue ether extracted and I isolated from the extract by aqueous sodium hydroxide (3%). The alkali-insoluble product in the ether extract gave unreacted methyl ether XIX (0·12 g). The alkaline extract was acidified and the product redissolved in ether–benzene and washed acid free and crystallized from benzene, yielding I as pale brown needles, m.p. 190° (previous shrinking at 187°), yield 0·06 g. (Found: C, 75·4; H, 6·0. $C_{16}H_{16}O_2$ requires: C, 75·0; H, 6·3%). The yield of I was 58% based on the recovery of unreacted XIX (alkali-insoluble product). The U.V. absorption spectrum of I (ethanol) revealed the following principal maxima: λ_{max} 250, 292 mμ (log ε = 4·146, 3·929).

7-*Methoxy*-1,2,3,4-*tetrahydrodibenzofuran* (XXII). Amalgamated zinc was prepared by shaking for 5 min mossy zinc (3 g), mercuric chloride (0·3 g) water (10 cc) and conc HCl (1–2 cc). The supernatant solution was decanted and III (0·2 g) dissolved in toluene (20 cc) added with conc HCl (3 cc). The mixture was refluxed for 21 hr with further additions of 3 cc lots of conc HCl at intervals of 3 hr. The reduction product isolated by ether extraction, on distillation at 128–132°/1·5 mm gave XXII as a colourless liquid 0·06 g, yield 32%). (Found: C, 76·9; H, 6·9. $C_{13}H_{14}O_2$ requires: C, 77·2; H, 6·9%). The U.V. absorption spectrum of XXII (ethanol) revealed the following principal absorption maxima: λ_{max} 258, 292 mμ (log ε = 4·138, 3·722).

Acknowledgements—Thanks are due to Sir Dorabjee Tata Trust, Government of Bombay, Lady Tata Memorial Trust and Council of Scientific and Industrial Research for financial assistance (to G. V. B. and N. L. T.) and to Dr. T. S. Gore for the microanalyses recorded in the paper.

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Tetrahedron, 1960, Vol. 10, pp. 230 to 237. Pergamon Press Ltd. Printed in Northern Ireland

SYNTHESIS OF HETEROCYCLIC STEROIDS—V*

ATTEMPTED SYNTHESIS OF B-NOR-6-AZA-6-METHYLEQUILENIN

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(*Received* 31 *March* 1960)

Abstract—Unsuccessful attempts have been made to synthesize the pyrrolo analogues of equilenin and 3-desoxyequilenin. The synthesis of several carbazole derivatives required in this connexion is described.

4-AZA[1] and 16-aza[2] analogues of steroids have been prepared by degradation of rings A and D in natural steroids and subsequent lactam formation. 17-a-Aza-D-homosteroids[3] have been prepared by Beckmann rearrangement of oximes of 17-ketosteroids. Pyridazenone analogues[4] have been synthesized by degradation of ring A in cholesterol and subsequent treatment with hydrazine, whereas the pyridyl steroids[5] have been synthesized from keto steroids by treatment with pyridyl lithium and hence the nitrogen atom does not form a part of the steroidal skeleton.[6]

Although I and II could not be synthesized, several new carbazole derivatives which were prepared in this connexion are now reported.

7-Methoxy-9-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole (III), starting material for the proposed synthesis of (I), was prepared as in Chart 1. Cyclization of IV gave a mixture of two isomers (A) and (B) represented as 7-methoxy-1-oxo-1,2,3,4-tetrahydrocarbazole (V) and 5-methoxy-1-oxo-1,2,3,4-tetrahydrocarbazole (VI). Since only (A) could be isolated in small quantity, the mixture was methylated and the products separated by chromatography. The two methylated products C and D may be represented as 7-methoxy-9-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole (III) and the corresponding 5-methoxy isomer (VII) respectively. Compound (A), on methylation, gives C. The latter on Wolff–Kishner–Huang-Minlon reduction gives E which on dehydrogenation with chloranil[7] yields F. Compound F has the same m.p. as 2-methoxy-9- methylcarbazole[8] (IX) and the two are identical. Consequently, compound A, C, D and E are assigned the structures V, III, VII, and VIII respectively.

In an attempt to convert III to B-nor-6-aza-6-methylequilenin (I) according to Johnson *et al.*[9], IV was converted to 9,10-dihydro-6-methoxy-4-methylcarbazolo-(2,1-d)-isoxazole (XI) through the intermediate 2-hydroxymethylene derivative (X) in the usual manner. The isoxazole (XI) was then isomerized in alkaline medium to

* Part IV: *Tetrahedron* **10**, 223 (1960).

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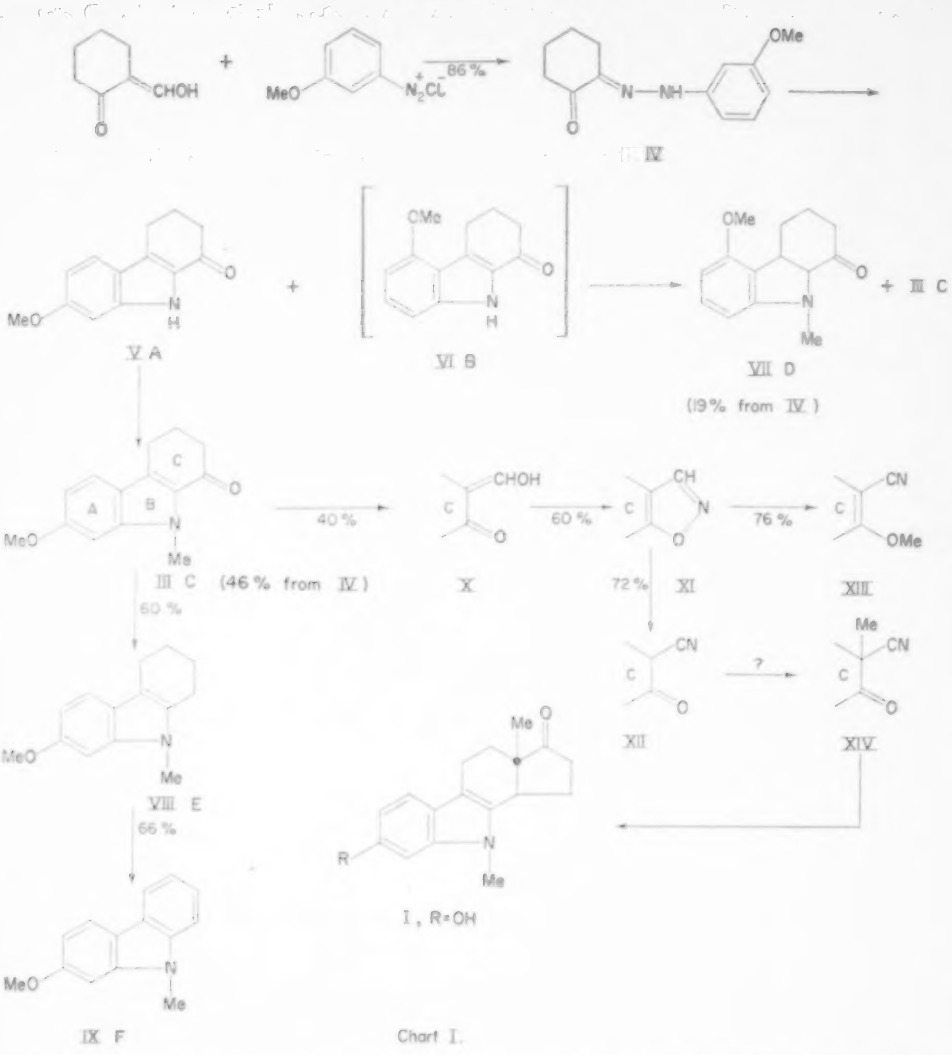


Chart I.

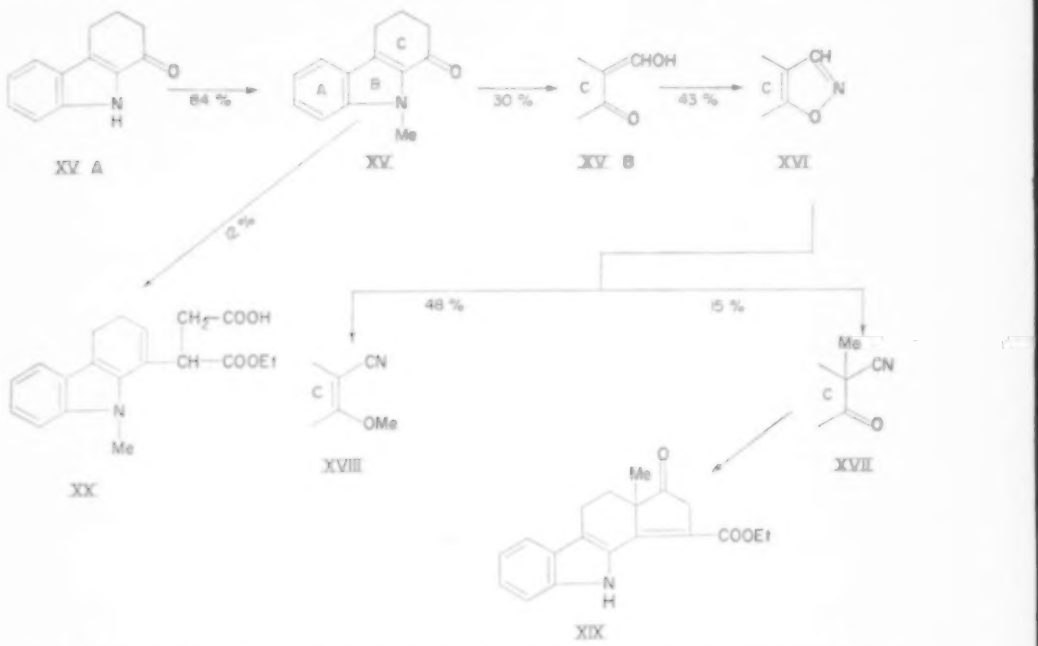
the alkali-soluble 2-cyano-7-methoxy-9-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole (XII) and methylated *in situ* yielding only 2-cyano-1,7-dimethoxy-7-methyl-3,4-dihydrocarbazole (XIII), instead of the desired 2-cyano-2,9-dimethyl-7-methoxy-1-oxo-1,2,3,4-tetrahydrocarbazole (XIV). We erroneously reported[10] as a C-methyl derivative (XIV), but the methoxyl value and the I.R. spectrum (strong band at 2222 cm^{-1} (4·5μ) indicating presence of a nitrile group in conjugation with a double bond) leaves no doubt, that the structure of XIII is an O-methyl ether (Fig. 1). All attempts to effect C-methylation of the intermediate cyano-ketone (XII) were unsuccessful.

The failure of the isoxazole (XI) to give the C-methyl-cyanoketone (XIV) is associated with the strong enolizability imparted to the ketonic function of the intermediate cyanoketone (XII) by the electron-donating N-methyl and 7-methoxy groups.

[10] G. V. Bhide, N. R. Pai, N. L. Tikotkar and B. D. Tilak, *Tetrahedron* **4**, 420 (1958).

It is interesting to record here that in the case of 1-oxo-9-methyl-1,2,3,4-tetrahydrocarbazole (XV), Stobbe reaction was successful (see later), although here the major product of methylation of isoxazole was the O-methylated derivative. It, therefore, appears that the 1-oxo function in these compounds possess pronounced enolic activity.

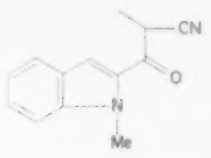
Attempts were made to isomerize the O-methyl derivative (XIII) to the C-methyl derivative (XIV) but without success.



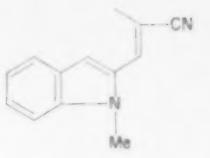
In view of the formation of isomers such as V and VI, experiments were carried out earlier with 1-oxo-1,2,3,4-tetrahydrocarbazole (XV A[11]). The latter was converted to the N-methyl derivative (XV) and through Johnson's equilenin synthesis to the isoxazole (XVI). Isomerization of the latter followed by methylation *in situ* gave 2-cyano-2,9-dimethyl-1-oxo-1,2,3,4-tetrahydrocarbazole (XVII) along with the isomeric 2-cyano-1-methoxy-9-methyl-3,4-dihydrocarbazole (XVIII) in larger yield. The structure of the above products was proved by estimation of methoxyl groups and the study of their I.R. spectra. The compound XVII showed bands at 1665 and 2240 cm^{-1} characteristic of the keto group conjugated with an aromatic residue as in G and of the weak nitrile group respectively (Fig. 2). The compound XVIII, on the other hand, gave a strong band at 2230 cm^{-1} indicating the presence of a nitrile group in conjugation with a double bond as shown in H (Fig. 3).

The methyl-keto-nitrile (XVII) was then subjected to Stobbe condensation with diethyl succinate under various experimental conditions wherein the relevant factors such as the amount of condensing agent (potassium-butoxide), the time and temperature of the reaction were altered. However, the Stobbe reaction failed XVII being

[11] A. Kent, *J. Chem. Soc.* 976 (1935).



G



H

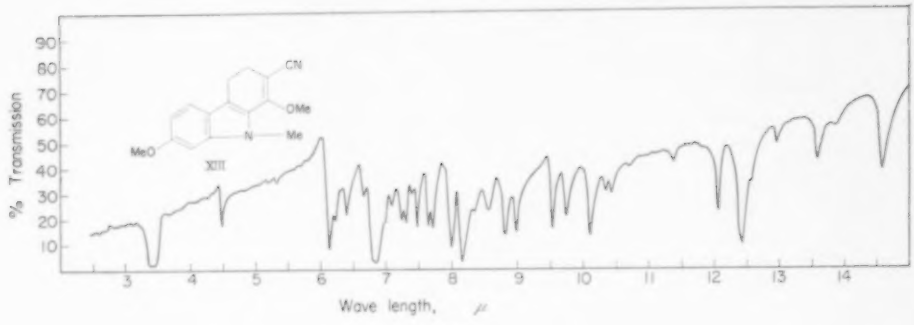
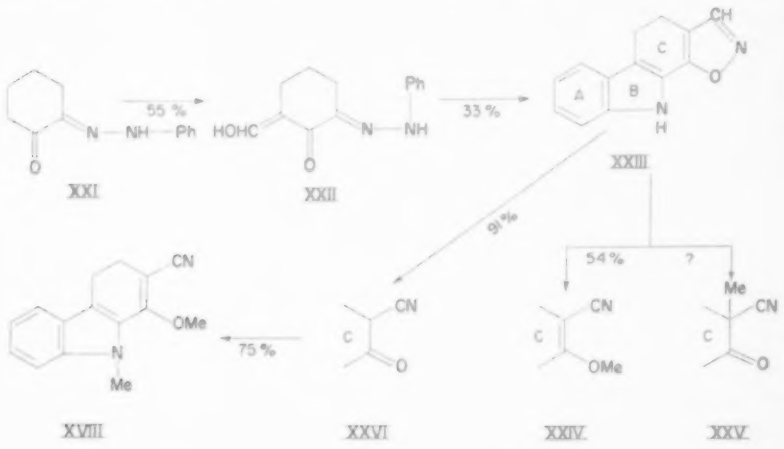


FIG. 1.

recovered unchanged. This failure may be due to the inaccessibility of the 1-oxo-group since XV undergoes a Stobbe condensation to yield β-carbethoxy-β-(3,4-dihydro-9-methylcarbazolyl-1)-propionic acid (XX) although the yield is low.



A new approach was explored wherein the N-methyl group in XVII was deleted, making the 1-oxo-group more accessible for the Stobbe condensation. Formylation of cyclohexane-1,2-dione-monophenylhydrazone[12] (XXI) yielded 3-hydroxymethylene-2-oxo-cyclohexanone-phenylhydrazone (XXII). Interaction of the latter with hydroxylamine hydrochloride afforded 9,10-dihydrocarbazolo-(2,1-d)-isoxazole (XXIII), the isoxazole and the carbazole rings being built up simultaneously. Treatment of XXIII with potassium butoxide followed by methyl iodide gave the O-methyl

[12] H. K. Sen and S. K. Ghosh, *J. Ind. Chem. Soc.* **4**, 477 (1927).

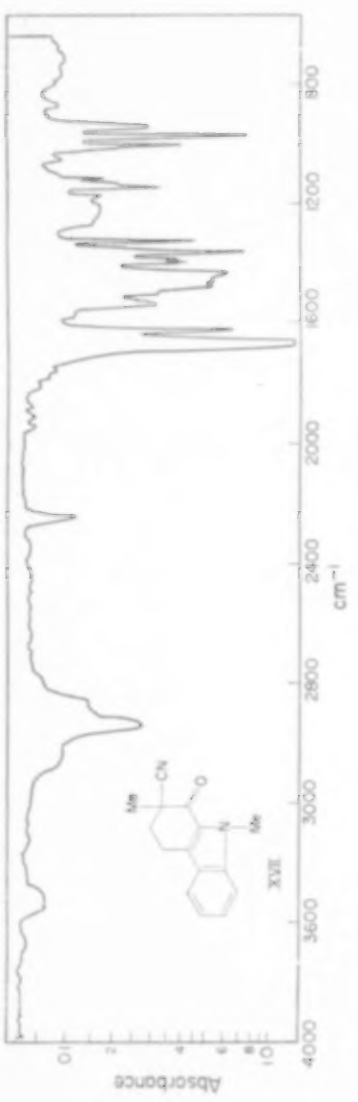

Absorbance
0
2
4
6
8
10
4000
3600
3000
2800
2400
2000
1600
1200
800
cm⁻¹
CN
O
Me
N
Me
XVII

Fig. 2.

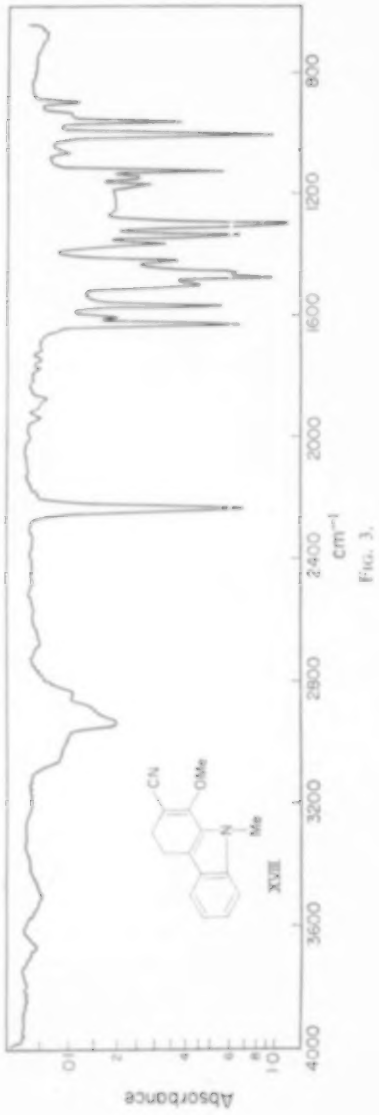

Absorbance
0
2
4
6
8
10
4000
3600
3200
2800
2400
2000
1600
1200
800
cm⁻¹
CN
OMe
N
Me
XVIII

Fig. 3.

derivative, 2-cyano-1-methoxy-3,4-dihydrocarbazole (XXIV) instead of the desired 2-cyano-2-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole (XXV). The isoxazole (XXIII) was then isomerized to 2-cyano-1-oxo-1,2,3,4-tetrahydrocarbazole (XXVI) and treated with excess of methyl iodide yielding exclusively 2-cyano-1-methoxy-9-methyl-3,4-dihydrocarbazole (XVIII) obtained earlier.

This synthesis of II (R = H) was, therefore, also unsuccessful due to the enolizability of the ketonic function in compound XXVI.

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EXPERIMENTAL

Cyclohexane-1,2-dione-mono-m-methoxyphenylhydrazone (IV). A solution of sodium acetate (25 g) in water (75 cc) was added to a solution of 2-hydroxymethylenecyclohexanone[6] (12·6 g) in methyl alcohol (150 cc). *m*-Anisidine (12·3 g) was diazotized at 0–5° with sodium nitrite (8·7 g) and conc HCl (27 cc), and the resulting solution (250 cc) added gradually during 30 min to the solution of 2-hydroxymethylene-cyclohexanone under mechanical agitation. The precipitate which separated was filtered and washed acid-free. The product crystallized from ethanol in brown needles, m.p. 173° (20 g, yield 86%) (Found: C, 67·2; H, 6·7; N, 11·7. $C_{13}H_{16}O_2N_2$ requires C, 67·2; H, 6·9; N, 12·1%).

7-*Methoxy*-1-*oxo*-1,2,3,4-*tetrahydrocarbazole* (V, A). Compound IV (2 g) was added to boiling glacial acetic acid (12 cc), conc HCl (3 cc) added through reflux condenser and the solution boiled for 5 min, and then diluted with boiling water (75 cc). The mixture was cooled and filtered and the residue washed and dried (1·6 g). The product (mixture of V and VI), on crystallization from aqueous acetone, gave a compound, m.p. 120–132°, which after repeated crystallization from aqueous acetone gave colourless needles, m.p. 156° of (V, A, 0·8 g) (Found: 72·6; H, 6·1; N, 6·2. $C_{13}H_{13}O_2N$ requires: C, 72·6; H, 6·0; N, 6·5%).

7-*Methoxy*-9-*methyl*-1-*oxo*-1,2,3,4-*tetrahydrocarbazole* (III, C) *and* 5-*methoxy*-9-*methyl*-1-*oxo*-1,2,3,4-*tetrahydrocarbazole* (VII, D). The mixture of above isomeric tetrahydrocarbazoles (2·1 g) was methylated by treatment with dimethyl sulphate (1.3 g) and fused potassium carbonate (5 g) in boiling acetone (30 cc) for 6–8 hr. The product was chromatographed over activated alumina using benzene as eluent giving two bands: one with violet and the other with green fluorescence in U.V. light. The band giving green fluorescence, on removal of benzene, gave (VII, D, 0·49 g) which crystallized from aqueous acetone in colourless needles, m.p. 104° (Found: C, 73·8; H, 6·5; N, 5·8, $C_{14}H_{15}O_2N$ requires: C, 73·4; H, 6·5; N, 5·8%). The band giving violet fluorescence gave (III, C, 1·2 g) which crystallized from aqueous acetone in colourless needles, m.p. 130° (Found: C, 73·3; H, 6·8; N, 5·9; OMe, 13·3. $C_{14}H_{15}O_2N$ requires: C, 73·4; H, 6·5; N, 5·8; OMe, 13·5%).

7-*Methoxy*-9-*methyl*-1,2,3,4-*tetrahydrocarbazole* (VIII, E). A mixture of III (C) m.p. 130° (0·46 g), potassium hydroxide (0·38 g), ethylene glycol (3 cc) and hydrazine hydrate (0·4 cc, 85%), was refluxed at 180° in an oil bath for 2 hr. Water formed in the reaction was removed by raising the temperature from 180° to 200°, in 30 min. The residual mixture was then refluxed at 200–210°, for 3 hr more. The resulting mixture was diluted with water (150 cc) and kept overnight. The reaction product crystallized from aqueous methyl alcohol in pale blue needles, m.p. 94° (0·26 g) (Found: C, 78·2; H, 8·3; N, 6·3. $C_{14}H_{17}ON$ requires: C, 78·1; H, 7·9; N, 6·5%).

2-*Methoxy*-9-*methylcarbazole* (IX, F). Chloranil (0·492 g), was added to a solution of (VIII, E, 0·215 g) in thiophene-free xylene (6 cc) and the mixture was heated under reflux at 150–160° in an oil bath for 2 hr, The reaction product on crystallization from methanol gave colourless needles, m.p. 100° of IX F, (0·14 g) (Lit,[8] m.p. 104°) (Found: C, 79·6; H, 6·1; N, 6·8. Calc. for $C_{14}H_{13}ON$: C, 79·6; H, 6·2; N, 6·6%).

2-*Hydroxymethylene*-7-*methoxy*-9-*methyl*-1-*oxo*-1,2,3,4-*tetrahydrocarbazole* (X). A solution of ethyl formate (1·4 cc) in dry ether (20 cc) was added to dry sodium methoxide (from 0·4 g of sodium). A solution of III (0·92 g) in dry ether (100 cc) was then added, the reaction flask filled with nitrogen, stoppered and the mixture shaken mechanically for 4 hr. The precipitate which separated was shaken with ether and the sodium salt of X was extracted with water (300 cc) and then with 5% NaOH (200 cc). Both water and alkaline extracts were mixed, cooled and acidified with cold dil HCl (1:1), and the precipitate filtered, washed and dried. The product, on crystallization from pet ether (b.p. 68–70°), gave shining yellow needles, m.p. 85–88° (0·41 g) (Found: 71·3; H, 6·1; N, 5.6. $C_{15}H_{15}O_3N$ requires: C, 70·0; H, 5·8; N, 5·4%).

9,10-*Dihydro*-6-*methoxy*-4-*methylcarbazolo*-(2,1-d)-*isoxazole* (XI). Dry finely powdered hydroxylamine hydrochloride (0·361 g) was added to a solution of X (0·61 g) in glacial acetic acid (12 cc) and the mixture was refluxed for 20 min by heating in an oil bath at 170–175°. After dilution with boiling water (10 cc), the mixture was cooled and more water added (40–50 cc) and left overnight in the refrigerator. Crystallization of the product from aqueous methanol gave XI as pale brown needles, m.p. 130° (0·36 g) (Found: C, 70·6; H, 5·1; N, 11·2. $C_{15}H_{14}O_2N_2$ requires: C, 70·9; H, 5·5; N, 11·0%).

2-*Cyano*-1:7-*dimethoxy*-9-*methyl*-3,4-*dihydrocarbazole* (XIII). To a solution of potassium (0·246 g) in t-butanol, XI (0·5 g) was added and the mixture boiled for 2 hr. After cooling, methyl iodide (0·5 cc) was added and the mixture kept at room temp for 2 hr and then refluxed gently for another 2 hr. After cooling, methyl iodide (1 cc) was added and the mixture refluxed for 2 hr, cooled and methyl iodide (0·5 cc) added and the mixture left overnight at room temp. The mixture was finally boiled for 4 hr and t-butanol removed (reduced press). The residue extracted with ether and washed with 2% aqueous sodium hydroxide. Removal of ether gave XIII (0·4 g) which crystallized from ethanol (violet fluorescence) in pale yellow needles, m.p. 156° (Found: C, 71·6; H, 6·0; N, 10·4; OMe, 30·9. $C_{16}H_{16}O_2N_2$ requires; C, 71·6; H, 6·1; N, 10·4; OMe 23·1%). The higher methoxyl value for XIII appears to be due to splitting of the N-methyl group, although methoxy group estimation in 9-methyl-1-oxo-1,2,3,4-tetrahydracarbazole (XV) and 7-methoxy-9-methyl-1-oxo-1,2,3,4-tetrahydracarbazole (III C) indicates that in these cases N-methyl group does not undergo fission during methoxy group estimation.

2-*Cyano*-7-*methoxy*-9-*methyl*-1-*oxo*-1,2,3,4-*tetrahydrocarbazole* (XII). To a solution of potassium (0·52 g) in t-butanol (40–50 cc), the isoxazole XI (1·03 g) was added and the mixture refluxed at 120–130° for 4 hr, then cooled and t-butanol removed (reduced press). The residue was extracted with ether and XII extracted with 3% aqueous sodium hydroxide (200 cc). Acidification of the alkaline extract gave a product which crystallized from aqueous methanol in pale brown needles, m.p. 221° (0·74 g, yield 72%) (Found: C, 71·4; H, 4·9; N, 10·3. $C_{15}H_{14}O_2N_2$ requires: C, 70·9; H, 5·5; N, 11·0%).

9-*Methyl*-1-*oxo*-1,2,3,4-*tetrahydrocarbazole* (XV). A mixture of dimethyl sulphate (0·77 cc), 1-oxo-1,2,3,4-tetrahydrocarbazole (XV A, 1 g),[11] anhydrous potassium carbonate (1·5 g) and acetone (25 cc) was refluxed for 6 hr. The product on crystallization from aqueous acetone, gave fine pale yellow needles of (XV, 0·9 g) m.p. 101° (Found: C, 78·8; H, 6·6; N, 6·9; OMe, 0·8. $C_{13}H_{13}ON$ requires: C, 78·4; H, 6·5; N, 7·0; OMe, nil%).

β-Carbethoxy-β-(3,4-*dihydro*-9-*methylcarbazolyl*-1)-*propionic acid* (XX). To a solution of potassium (0·45 g) in t-butanol (10–12 cc), diethyl succinate (3·2 cc) and XV (1 g) were added and the flask filled with nitrogen and stoppered. The mixture was shaken mechanically for 5–6 hr. The mixture was cooled and acidified in cold with dil HCl. t-Butanol was removed under reduced pressure and the residue was extracted with ether. The ether solution was washed, acid-free and then extracted twice with 15 cc portions of 2% ammonia. The ammonical extract was acidified carefully with cold dil HCl and the mixture kept overnight. The product XX was crystallized from ethanol as greenish yellow rhombic plates, m.p. 174° (0·165 g, yield 12%) (Found: C, 69·4; H, 6·1; N, 4·4. $C_{19}H_{21}O_4N$ requires: C, 69·7; H, 6·4; N, 4·3%).

2-*Hydroxymethylene*-2-*methyl*-1-*oxo*-1,2,3,4-*tetrahydrocarbazole* (XV B). A solution of ethyl formate (1·5 cc) in dry benzene (10 cc) was added to dry sodium methoxide (from 0·414 g of sodium). Finely powdered XV (1·2 g) was then added followed by benzene (80 cc). After replacing the air by nitrogen, the flask was stoppered and shaken for 6 hr with formation of yellowish green precipitate. The mixture was cooled, 40% aqueous sodium hydroxide (5 cc) added and the mixture extracted with ether. Ether extract was washed with water (300–400 cc) and then once with 2% aqueous sodium hydroxide (100 cc). Both the alkaline extracts were acidified with cold dil HCl. The product which separated crystallized from pet ether (b.p. 68–70°) in pale yellow needles, m.p. 81–83° (0·4 g) (Found: C, 73·3; H, 5·2; N, 6.6. $C_{14}H_{13}O_2N$ requires: C, 74·0; H, 5·1; N, 6·1%).

9,10-*Dihydro*-4-*methylcarbazolo*-(2,1-d)-*isoxazole* (XVI). Dry finely powdered hydroxylamine hydrochloride (0·25 g) was added to a solution of XV B (0·8 g) in glacial acetic acid (37 cc) and the mixture refluxed for 10 min at 140–155°. The mixture was cooled to 100° and immediately diluted with boiling water (100 cc), cooled and kept overnight in the refrigerator. The product was filtered, washed, extracted with ether and the extract washed with 2% aqueous sodium hydroxide till free from alkali-soluble products. The product, obtained on removal of ether, crystallized from aqueous

methanol in pale brown needles, m.p. 109° (0·34 g) (Found: C, 74·3; H, 5·2; N, 12·4. $C_{14}H_{12}ON_2$ requires: C, 75·0; H, 5·4; N, 12·5%).

2-*Cyano*-2,9-*dimethyl*-1-*oxo*-1,2,34-*tetrahydrocarbazole* (XVII) and 2-cyano-1-m*ethoxy*-9-*methyl*-3,4-*dihydrocarbazole* (XVIII). To a solution of potassium (0·44 g) in t-butanol, the isoxazole (XVI, 0·83 g) was added, and the mixture boiled for 1 hr. The mixture was then treated with small portions of methyl iodide as in the synthesis of XIII using in all 3 cc of methyl iodide. t-Butanol was finally removed under reduced pressure and the residue extracted with ether. Ether extract was washed with 2% aqueous sodium hydroxide. Removal of ether and crystallization of the product from aqueous ethanol, yielded both XVII and XVIII. The mixture was chromatographed on a cellulose (Whitman, Grade I) pulp column and the column eluted with benzene–pet ether (60–68°). Two distinct bands were obtained, one showing violet and the other pale blue fluorescence in U.V. light.

After removal of the solvent, the pale blue fluorescent band gave XVII which crystallized from aqueous ethanol in yellowish rhombs, m.p. 96° (0·12 g) (Found: C, 75·6; H, 5·7; N, 11·8; OMe, 0·8. $C_{13}H_{14}ON_2$ requires: C, 75.6; H, 5·9; N, 11·8% OMe, nil).

The band showing violet fluorescence, gave XVIII which crystallized from aqueous ethanol in shining white needles, m.p. 122° (0·42 g) (Found: C, 75·6; H, 5·7; N, 11·8; OMe, 13·8. $C_{13}H_{14}ON_2$ requires: C, 75·6; H, 5·9; N, 11·8; OMe, 13·6%).

3-*Hydroxymethylene*-2-*oxo*-*cyclohexanone*-*phenylhydrazone* (XXII). A mixture of sodium methoxide (from 0·138 g of sodium), ethyl formate (0·5 cc), cyclohexanone-1,2-dione-monophenyl-hydrazone[12] (0·404 g) and dry benzene (35 cc) was shaken mechanically for 5 hr under nitrogen. The initial pale yellow colour of the solution changed to blood red and a precipitate of the sodium salt of XXII separated out. The mixture was extracted with ether and XXII was removed by shaking with 2% aqueous sodium hydroxide (90 cc) in three lots. Acidification of the extract, gave a product, which on crystallization from aqueous ethanol, gave XXII as purple plates, m.p. 153° (0·25 g) (Found: C, 67·7; H, 6·0; N, 12·1. $C_{13}H_{14}O_2N$ requires: C, 67·8; H, 6·1; N, 12·2%).

9,10-*Dihydrocarbazolo*-(2,1-d)-*isoxazole* (XXIII). Dry finely powdered hydroxylamine hydrochloride (1·675 g) was added to a solution of XXII (2·7 g) in glacial acetic aicd (110 cc) and the mixture was heated under reflux for 30 min at 155–165°. After dilution with hot water (300 cc), the mixture was cooled, extracted with ether and the extract washed with 2% aqueous sodium hydroxide. The. product crystallized from aqueous methanol in dark brown needles, m.p. 196° (0·8 g) (Found: C, 74·5; H, 4·5; N, 13·6. $C_{13}H_{10}ON_2$ requires: C, 74·3; H, 4·8; N, 13·3%).

2-*Cyano*-1-*methoxy*-3,4-*dihydrocarbazole* (XXIV). To a solution of potassium (0·14 g) in t-butanol (15 cc), XXIII (0·8 g) was added and the mixture boiled for 2 hr. After cooling methyl iodide (0·213 cc) was added and the flask stoppered and shaken for 5 hr and kept overnight. The mixture was then refluxed at 120–125° for 4 hr and cooled. t-Butanol was removed under reduced pressure and the residue extracted with ether and the extract washed with 2% aqueous sodium hydroxide. Removal of ether, gave XXIV, which crystallized from aqueous methanol in pale brown needles, m.p. 144° (0·46 g) (Found: C, 74·5; H, 4·9; N, 13·0; OMe, 14·8. $C_{14}H_{12}ON_2$ requires: C, 75·0; H, 5·3; N, 12·5; OMe, 13·8%).

2-*Cyano*-1-*oxo*-1,2,3,4-*tetrahydrocarbazole* (XXVI). To a solution of potassium (0·6 g) in t-butanol (25–30 cc), XXIII (1·1 g) was added and the mixture refluxed at 120–130 for 2 hr. The ether solution of the reaction product was extracted with 2% aqueous sodium of hydroxide. Acidification of the alkaline extract gave a product which crystallized from aqueous methanol in brown needles, m.p. 233° (1·0 g, yield 91%) (Found: C, 73·8; H, 4·4; N, 14·1. $C_{13}H_{10}ON_2$ requires: C, 74·3; H, 4·7; N, 13·3%).

Acknowledgements—Thanks are due to Sir Dorabjee Tata Trust, Government of Bombay, Lady Tata Memorial Trust and Council of Scientific and Industrial Research, for financial assistance (to G. V. B. and N. L. T.), and to Dr. T. S. Gore for the microanalyses recorded in the paper.

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Tetrahedron, 1960, Vol. 10, pp. 238 to 243. Pergamon Press Ltd. Printed in Northern Ireland

STEROIDAL SAPOGENINS—LXII

12-METHYL HEMIKETALS DERIVED FROM 12-KETO-16-DEHYDROPREGNENES[1]

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(*Received* 18 *February* 1960; *in revised form* 8 *April* 1960)

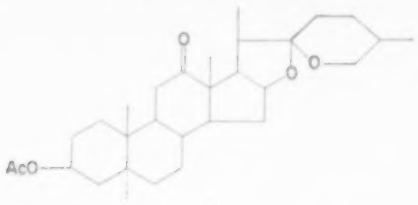
Abstract—Large-scale degradation of the sidechains of the 12-ketosapogenins, hecogenin and gentrogenin, gave respectively 3β-acetoxy-5α,16-pregnene-12,20-dione and 3β-acetoxy-5,16-pregnadiene-12,20-dione. Methanol crystallization of the *crude* enones gave in small yield the crystalline hemiketals, 3β-acetoxy-12β-hydroxy-12α-methoxy-5α,16-pregnen-20-one and 3β-acetoxy-12β-hydroxy-12α-methoxy-5,16-pregnadien-20-one. The hemiketals exist largely in a hydrogen-bonded state. Their structure proof and infrared and ultraviolet spectra are discussed in detail.

SEVERAL years ago, Cameron *et al.* briefly described in the experimental section of their paper[3] a compound which they thought might be a 12-hemiketal derived from 3β-acetoxy-5α,16-pregnene-12,20-dione. They were unable to repeat their preparation. During the course of the sidechain degradation of hecogenin(I) and gentrogenin(II) to yield 3β-acetoxy-5α,16-pregnene-12,20-dione(III) and 3β-acetoxy-5,16-pregnadiene-12-20-dione(IV), respectively, we have been able to isolate consistently the corresponding hemiketals, viz. 3β-acetoxy-12β-hydroxy-12α-methoxy-5α,16-pregnen-20-one(V) and 3β-acetoxy-12β-hydroxy-12α-methoxy-5,16-pregnadiene-20-one(VI). The hemiketals V and VI have interesting spectral properties. In this paper we wish to report in detail the preparation, structure proof and the ultraviolet and infrared absorption spectra of V and VI.

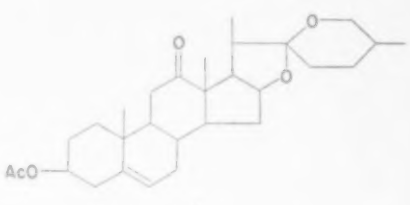
Degradation of the 12-ketonic sapogenins, I and II was carried out by an improved procedure which gives maximal yields of 16-dehydro-12,20-pregnenes (cf. experimental). The three step sidechain degradation sequence was ordinarily carried out without isolation of intermediates until the final purification of the desired 16-dehydro-12,20-pregnenes, III and IV. The hemiketals V and VI were *obtained only from non-isolation sequences* (*cf.* Experimental section). The sidechain degradation procedure (described in detail in the experimental section) involved conversion of the sapogenins to pseudosapogenin diacetates with acetic anhydride containing 0·1 per cent acetic acid;[4] oxidation of the latter with chromium trioxide in acetic acid at low temperatures using dichloroethane as co-solvent to give 16β-acyloxy-12,20-oxosteroids; and acetic acid cleavage of the 16-acyloxy substituent[3] to give the enones III and IV. Each step in this sequence could be interrupted to yield the crystalline intermediate. The crude enones III and IV obtained in non-isolation sequences were purified by chromatography on florisil. On crystallization from methanol the pure

[1] Previous paper in this series: Steroidal Sapogenins—LXI
[2] Eastern Utilization Research and Development Division, Agricultural Research Service, United States Department of Agriculture.
[3] A. F. B. Cameron, R. M. Evans, J. C. Hamlet, J. S. Hunt, P. G. Jones and A. G. Long, *J. Chem. Soc.* 2807 (1955).
[4] M. E. Wall and S. Serota, *J. Amer. Chem. Soc.* **79**, 6481 (1957).

enones III and IV were obtained. Usually several crystalline crops were obtained rapidly. The residual syrupy mother liquors on long standing in the refrigerator slowly deposited further crystalline material. These latter crops contained largely the hemiketals V and VI mixed with the enones III and IV. The hemiketals were easily purified by crystallization.



I



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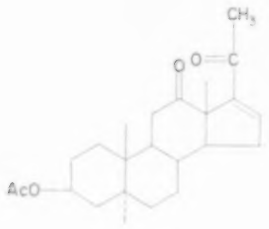
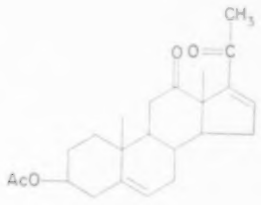
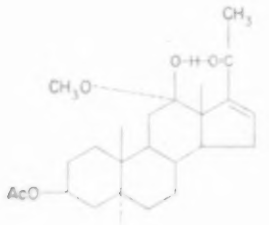


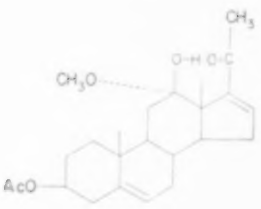
III



IV



V



VI

Structure proof of V and VI was based on the following evidence given in detail for V, that of VI following closely similar lines. Carbon, hydrogen and methoxyl values were in agreement with the assigned structure. The molecular rotation of the hemiketal V exhibited a large negative shift in comparison with that of the corresponding enone, III. Since 12-keto groups make a strong positive contribution to the total molecular rotation,[5] the large negative shift is consistent with the disappearance of the 12-ketone moiety. Similarly the analysis of the ultraviolet spectrum of the hemiketal leads to the same conclusion. Thus steroids with the Δ^{16}-20-oxo grouping and no substituent at C_{12} generally show a maximum at 239–242 mμ.[6] The presence of a 12-ketone brings about an hypsochromic shift to 227–229 mμ[7,8] which has been

[5] D. H. R. Barton and W. Klyne, *Chem. & Ind.* 755 (1948).
[6] L. Dorfman, *Chem. Rev.* **53**, 47 (1953).
[7] G. P. Mueller, R. E. Stobaugh and R. S. Winniford, *J. Amer. Chem. Soc.* **75**, 4888 (1953).
[8] M. E. Wall, H. E. Kenney and E. S. Rothman, *J. Amer. Chem. Soc.* **77**, 5665 (1955).

ascribed to the increased energy of excitation in going from the ground state to a state wherein the dipoles of both excited carbon–oxygen systems are opposed.[7] The hemiketal V exhibits an ultraviolet maximum at 242 mμ again indicating absence of the 12-ketone and presence of the conjugated Δ^{16}-20-ketone moiety. The infrared spectrum of the hemiketal V provided excellent proof of both the overall structure and the stereochemistry at C_{12}. A very intense band was observed in carbon bisulfide solution at 3340 cm^{-1}. Successive dilutions did not change the position of the

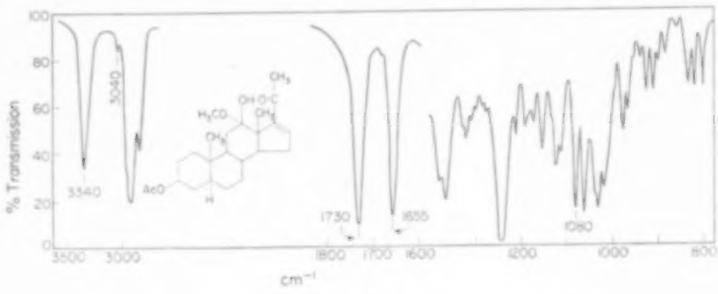


FIG. 1.

absorption band or the relative intensities, indicating that we are dealing with an intramolecular bonded hydroxyl group. The degree of hydrogen bonding exhibited is indeed unique. Thus compound V has an absorption band at 3340 cm^{-1} with an apparent molecular extinction of 189·5. By comparison the strongly hydrogen bonded 20-hydroxy-tigogenin[9] acetate has a band at 3520 cm^{-1}, apparent molecular extinction 101·6; and a typical unbonded hydroxyl, as is the 3β-hydroxyl moiety in sarsasapogenin, exhibits an absorption band at 3620 cm^{-1}, apparent molecular extinction 41·6. In the carbonyl region the infrared spectrum of II shows two strong peaks, 1732 cm^{-1}, acetate, and 1655 cm^{-1}, conjugated 20-ketone The normal location for the latter band in C-ring unsubstituted steroids is 1666–1670 cm^{-1}.[10] whereas in the case of Δ^{16}-12,20-diketones the location is at 1678 cm^{-1}.[10] The direction of the shift observed in the location of the conjugated 20-ketone in V is in accord with previous observations of the effect of hydroxyl groups hydrogen bonded to ketones. Thus Jones *et al.*[11] found in the case of 17-hydroxy-20-ketones which exhibit only partial hydrogen bonding that the location of the 20-ketone band shifted in part from 1708 cm^{-1} which is normal to 1693 cm^{-1}. Rothman and Wall[12] have observed a similar shift with 17α-hydroxy-12,20-diketones. We conclude therefore from the evidence just presented that practically complete hydrogen bonding of the hydroxyl group in V with the conjugated ketone has occurred. This can take place only if the hydroxyl grouping has the equatorial 12β-orientation. A strong band is present at 1082 cm^{-1} and completely absent in the infrared spectrum of the enone III. From the studies of Page[13] this band should be due to an axial methoxy group, the equatorial methoxy showing a band at 1100 cm^{-1}. According to the classic "rule of the rear,"[14]

[9] M. E. Wall and H. A. Walens, *J. Amer. Chem. Soc.* **80**, 1984 (1958).
[10] R. N. Jones and F. Herling, *J. Org. Chem.* **19**, 1252 (1954).
[11] R. N. Jones, P. Humphries, F. Herling and K. Dobriner, *J. Amer. Chem. Soc.* **74**, 2820 (1952).
[12] E. S. Rothman and M. E. Wall, *J. Amer. Chem. Soc.* **77**, 2229 (1955).
[13] J. E. Page, *J. Chem. Soc.* 2017 (1955).
[14] T. F. Gallagher and T. H. Kritchevsky, *J. Amer. Chem. Soc.* **72**, 882 (1950).

attack by methanol on the C_{12} carbonyl moieties of the enones III or IV should lead to the stereochemistry shown for the products V and VI, i.e. 12α-methoxy-12β-hydroxy. Molecular models of the hemiketals V and VI indicate that strong hydrogen bonding should occur between the 12β-hydroxyl and the 20-ketone moieties. The infrared spectra of V and VI indicate that these compounds exist largely in the hydrogen bonded state. The strong hydrogen bonding may account for the stabilization of the hemiketals, allowing their isolation under appropriate conditions.

The hemiketals V and VI were obtained consistently as by-products from 100 g sapogenin sidechain degradation runs, usually yielding 1·0–2·0 g of crystalline hemiketal. The enones III and IV were obtained in 50–70 per cent yield. The syrupy mother liquors which yield the hemiketals enable one to obtain a much higher concentration of the enones III and IV in methanol at refrigerator temperatures than is possible with the pure enones. This suggested the possibility that the hemiketal could be made from a pure enone and methanol in concentrated solution by use of an appropriate co-solvent.[15] With use of small quantities of methylene chloride, a 10 per cent solution of III in methanol remained in solution at 5°. After 8 days, infrared analysis of a sample indicated that a mixture consisting of 40 per cent III and 60 per cent V had been formed. Another sample taken after 17 days gave the same results. Hence, under experimental conditions which prevent removal of the hemiketal by crystallization, the reaction of the enone, III, with methanol results in an equilibrium mixture of III and V in a 2 : 3 ratio. The mixture could be separated by fractional crystallization. It is of interest to note that methanol is routinely used as the crystallizing agent for the enone III. The combination of low concentrations, short time and increased temperature all tend to shift the equilibrium between enone and hemiketal to the enone.

The hemiketals are very unstable substances. At room temperature they slowly decompose over a period of several weeks to the corresponding enones. Heating at 70° quickly gives quantitative conversion to the enones. Hence, the melting points of the hemiketals are really those of the corresponding Δ^{16}-12,20-diketones III and IV. Treatment of the hemiketals with base in tertiary butanol gave the enones III and IV. With methanolic hydrochloric acid, the hemiketal V was converted to a mixture of III and the corresponding 16α-methoxy pregnane with infrared spectrum identical to that obtained by treating III with methanolic potassium hydroxide.[16] Acetylation of the hemiketal V with acetic anhydride in pyridine at room temperature gave starting material.

EXPERIMENTAL

3β-Acetoxy-5α,16-pregnene-12,20-dione (III)

100·0 g hecogenin acetate(I) was heated 17 hr at 180° with 250 ml acetic anhydride to which was added 0·1% glacial acetic acid. The reaction was conveniently carried out in a 2 l. resin flask made of thick walled pyrex glass with a teflon gasket between the upper and lower sections, the two sections being secured by a heavy duty clamp. The flask was provided with a magnetic stirrer and a thermometer. After cooling, 45 ml water was added to the reaction mixture to convert all the acetic anhydride to acetic acid. Sufficient acetic acid to bring the volume to 1·5 l. was added followed by 1·5 l. of dichloroethane. The single phase solution was cooled in an ice-salt bath to −8°. To the solution containing pseudo-hecogenin diacetate, was added over a period of 15 min a solution of 50·0 g chromium trioxide in 1·5 l. 90% acetic acid, precooled to +8°. The oxidation was allowed to proceed for

[15] We wish to thank Professor R. B. Turner of the Rice Institute, Houston, Texas, for this suggestion.
[16] D. K. Fukushima and T. F. Gallagher, *J. Amer. Chem. Soc.* **73**, 196 (1951).

another 60 min during which the temperature was kept at −2 to −5°. At the expiration of this time, excess oxidant was discharged by addition of 50·0 g sodium metabisulfite in 0·4 l. water, precooled to +2°. To the reaction mixture was added 5 l. 10% sodium chloride solution. The lower phase consisting largely of dichloroethane was withdrawn. The residual aqueous liquors were extracted 6 times with ¼ volumes of ether. The ethereal layers were combined with the dichloroethane. The organic layers were washed with sodium bicarbonate solution until neutral. The sodium bicarbonate solution was re-extracted with ether. All the organic layers were combined, dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residual glassy, crude "hecone" was refluxed 2 hr with 1 l. of glacial acetic acid, and then most of the acid was evaporated *in vacuo*. The residue was taken up in heptane, shaken with sodium bicarbonate solution and the heptane layer dried. The heptane solution of crude III was passed through a column containing 200 g of florisil. The column was then eluted with benzene. The solvents were combined, evaporated to dryness and the residue crystallized from methanol. Three crystalline crops, totalling 43·6 g were obtained m.p. 178–180° infrared spectrum identical to that of an authentic sample.[8]

3β-Acetoxy-12β-hydroxy-12α-methoxy-5α,16-pregnen-20-one (V)

The mother liquors from the preparation of the enone, III were concentrated and allowed to stand in the refrigerator. After one week, crystals were noted and after two weeks a crystalline crop of 2·0 g was obtained. The infrared spectrum indicated that a mixture consisting mainly of a new compound but also containing III had been obtained. On taking up the crystalline material in a small volume of dichloromethane and adding low boiling petroleum ether, pure V was obtained, m.p. 158–162° followed by resolidification and m.p. 180–180·5°, $[\alpha]_D^{25}$ −15°, (Found C, 71·51; H, 9·02; OCH_3, 8·2. $C_{24}H_{38}O_5$ requires: C, 71·25; H, 8·97; OCH_3, 7·7%). The ultraviolet spectrum, 0·04 g/liter in methanol shows a maximum band at 242 mμ, ε = 9,304. The infrared spectrum was obtained in carbon bisulfide solution, 10·0 g/l. Important bands are at 3340 (bonded hydroxyl) 3040 (C—H stretching due to HC—C—C—) 1730 (acetate), 1655 (conjugated carbonyl) and 1082 cm^{-1} (methoxyl).

Reaction of III *with methanol in presence of a co-solvent*

A solution of 0·5 g of the enone III was dissolved in 0·8 ml methylene chloride, mixed with 5 ml of methanol and stored in a stoppered flask at 5°. An aliquot was removed after 8 days and the solvent removed *in vacuo* in the absence of heat. The infrared spectrum of the sample indicated that a mixture of the enone III and the hemiketal V was present. In particular the infrared spectrum showed presence of bands at 1685 cm^{-1}, characteristic of the conjugated carbonyl moiety of III and at 1655 cm^{-1}, characteristic of the same grouping in V, the latter band being somewhat more intense than the former. The characteristic hydroxyl band of V at 3340 cm^{-1} was also present and was used to determine the percentage of V in the mixture. From these calculations it was estimated that the mixture contained 60% V and by difference 40% III. Calculations based on the intensities of the conjugated carbonyl bands were in rough agreement. After several crystallizations from methylene chloride and low boiling petroleum ether, pure V could be separated from III as described previously.

Effect of heat, alkali, and acid on hemiketal (V)

A sample of 100 mg V was allowed to stand at room temperature. Samples were analyzed by means of the infrared spectrum. Conversion of V to III could be estimated by means of the shift in location of the Δ^{16}-20-ketone band from 1655 cm^{-1} in V to 1680 cm^{-1} in III. Decomposition of V to III commenced in a few days and was almost complete in 2 weeks. A sample of V was heated 2 hr at 70°, infrared analysis showed complete conversion to III.

A solution of 0·2 g V in 10 ml t-butanol was stirred with a solution of 0·2 g potassium hydroxide in 0·24 ml water for 3 hr at 40°. On dilution with water and ether extraction, 3β-hydroxy-5α,16-pregnene-12,20-dione identical to an authentic specimen was the sole reaction product.

A solution of 0·1 g hemiketal V in 10 ml of methanol containing 0·1 ml of conc hydrochloric acid was allowed to stand at room temp for 4·5 hr. After neutralization of the acid with sodium bicarbonate the methanolic solution was diluted with water, extracted with ether and the solvent evaporated. The residual glass, 70 mg, was examined by infrared spectroscopy. The conjugated Δ^{16}-20-ketone had disappeared. The infrared spectrum was similar to that obtained by treating the enone III with

5% potassium hydroxide or hydrochloric acid in methanol. The product was therefore judged to be a mixture of III and the 3β-hydroxy-16α-methoxy-pregnene-12,20-dione obtained by the addition of CH_3OH to the Δ^{16}-double bond in the presence of acid or alkali. Under acidic conditions V → III which then forms the 16α-methoxy derivative.

3β-Acetoxy-5,16-pregnadiene-12,20-dione (IV)

In the same manner described above for the conversion of I to III, 100 g of gentrogenin acetate gave 35 g of IV, m.p. 172–173° the infrared spectrum was identical to that of an authentic specimen.[17]

3β-Acetoxy-12β-hydroxy-12α-methoxy-5,16-pregnadiene-20-one (VI)

The mother liquors remaining from the methanol recrystallization of IV were concentrated. After standing in the refrigerator for one week, 1·2 g of a crystalline product rich in the hemiketal fraction was isolated. On crystallization from dichloroethane-low boiling petroleum ether, the pure hemiketal VI was obtained, m.p. 165–175°, $[\alpha]_D^{25} - 86°$, λ max 241, $\varepsilon = 8654$, infrared spectrum similar in all important bands to that of hemiketal V. The infrared spectrum of VI is best distinguished from V by examination in the C—H stretching region, VI shows 5 bands and a shoulder between 3060–2800 cm^{-1} whereas V shows only 3 bands in this region. (Found C, 71·23; H, 8·50; OCH_3, 8·15; $C_{24}H_{34}O_5$ requires: C, 71·61; H, 8·51, OCH_3, 7·7).

[17] H. A. Walens, S. Serota and M. E. Wall, *J. Org. Chem.* **22**, 182 (1957).

Tetrahedron, 1960, Vol. 10, p. 244. Pergamon Press Ltd. Printed in Northern Ireland

BOOK REVIEW

MAX TISHLER (Editor-in-Chief): **Organic Syntheses** Vol. 39. John Wiley, New York; Chapman & Hall, London, 1959. 114 pp., $4.00.

IT is frequently the custom for a reviewer of a new volume of *Organic Syntheses* to greet it with appropriate rapture, list its contents, congratulate the Editors, and then bow out gracefully. The current volume undoubtedly fully merits plaudits as laudatory as those accorded its recent predecessors; prepared under the able editorship of Dr. Max Tishler, it maintains in excellent fashion those high standards of clarity and thoroughness in the description of experimental procedures which have characterized the earlier volumes of the series. Methods for the preparation of several compounds of considerable interest are described, including those for the preparation of tetracyanoethylene and triptycene. Nevertheless, in the opinion of this Reviewer, the time has come to make a reappraisal—an agonizing one, if necessary—of the continuing usefulness of the series in its present form. The early volumes of *Organic Syntheses* filled a very real need in providing excellent and well-tested experimental procedures for the preparation of many compounds of general interest and importance which were not then available commercially. However, within recent years the number of commercially available compounds has increased greatly. Further, the growth of *Organic Syntheses* has resulted in the coverage of many of the compounds of general interest which are still not available commercially. As a result of these circumstances, the compounds whose preparation is described in the more recent volumes have become increasingly esoteric, if not exotic. Thus, it seems that some change in policy might well be considered. For example, the frequency of appearance of new volumes might be reduced with the simultaneous imposition upon the contributors of more stringent standards of timeliness and general interest than those currently employed. Alternatively, annual publication might continue, but with a reduced number of contributions per volume, and the space thereby made free might be devoted to the listing of compounds which have become commercially available for the first time during the year of publication together with their sources (it may be noted that at least two of the compounds whose preparation is described in the present volume are thus available). Finally, it should be emphasized that it is in large measure the very success of *Organic Syntheses* which casts a shadow on its future, and that had not many distinguished chemists been willing to devote their time and skill in generous degree to this undertaking, we would be faced with a much more serious problem than that of the affluent literature.

PETER YATES

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